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(1) Stein, P., and Lowy, P., Am. Rev. Tuberc., 53:345, 1946.

(2) Curtis, H. G., and Browning, R. H., Ohio State M. J., 42:500, 1946.

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AUSCULTATION¹

A New Appraisal

F. M. POTTENGER²

Why is physical examination of the chest being neglected? Why do so many clinicians want to see an X-ray film before they make a physical examination of the chest? Is it because they lack confidence in physical examination? Will the roentgenogram give more information than they can obtain from a personal study of the patient? Will it give all the information desired? Or, does the fault lie in the uncertainty of the facts obtained by examining the chest by the eye, the ear and touch?

It is common knowledge that neither physical nor X-ray examination always reveals fully the pathological condition in the lungs. The one contains the elements of strength and weakness involved in a human study of a human being; the other, the accuracy and inaccuracy of a mechanical approach to the same. Neither procedure, in itself, is fully satisfactory, but they supplement each other. Tuberculosis is the most interesting chest disease to study by means of the physical senses because it exhibits every form of pathological process that involves the lungs and pleura—pneumonitis, bronchitis, emphysema, cavity, pleural inflammation and effusion (both simple and purulent), and pneumothorax.

Let us now inquire why physical examination is not more satisfactory.

Normal respiratory sounds: Most physicians depend more on auscultation than on other methods of physical examination but have difficulty in interpreting their findings. The reason for this difficulty is not hard to find if one compares auscultatory sounds as heard in chests with their description found in textbooks and taught to medical students.

The first basic error is the inaccurate description of the respiratory murmur itself. It is stated in textbooks that inspiration is to expiration as five to three, three to two, two to one, and so on, according to the authority consulted. Yet if one will listen carefully throughout the normal respiratory cycle, he will find there is very little difference in the length of inspiration and expiration. Inspiration is heard throughout the inspiratory phase, and expiration throughout expiratory phase.

Spirometric tracings made by Dr. Max Pinner³ and Dr. George C. Leiner on normal persons show that the expiratory phase of respiration is even longer than inspiration. The last aspect of restoring the lung to its resting phase may be scarcely audible or inaudible.

Pinner states: "In them [i.e. 6 normal persons] the average relative lengths of expiration to inspiration are as follows: 5.6:5.0; 6.0:5.0; 7.8:5.6; 6.4:4.6; 6.0:4.6; 8.0:5.0. The first figure refers to expiration and the second to inspira-

¹ Read in part at the annual meeting of the American Therapeutic Society at Atlantic City, May 10 to 12, 1946.

² The Pottenger Sanatorium and Clinic, Monrovia, California.

³ Personal communication.

tion in each case. As you see, the relation is consistent and the total average is 6.6:5.1."

The probable reason expiration is apparently shorter on stethoscopic records is that inspiration is a much more forceful act than expiration. While both inspiration and expiration take place as a result of muscular activity, the expiratory effort is normally weaker than the inspiratory. Part of expiration and the final settling of the lung to its resting condition are due to the restoration of pressure equilibrium between the intraabdominal and intrathoracic cavities. This latter is probably attended by very little force; in fact, is almost passive.

It is also taught that expiration follows immediately on inspiration in normal vesicular respiration but that there is a break between inspiration and expiration in bronchial breathing, whether found in normal or pathological chests. The facts are that this break may or may not be present in pathological chests. It is not a constant factor in pulmonary infiltrations.

Cause of respiratory sounds: An important error arises from considering the effect of the column of air on the respiratory passages as the main factor in producing the respiratory murmur. I questioned this in my early writings (1).

Laennec (2) stated: "The sound of respiration presents different characters according as it takes place in the pulmonary tissue, the larynx, the trachea, or the large bronchial trunks." He believed the sounds are produced by the air stream pressing against the trachea, bronchi and alveoli. He described the vesicular murmur as "a gentle but distinct murmur which indicates the penetration of air into the pulmonary tissue and its expulsion." He recognized bronchial breathing as being heard normally in the first interspace and over the superior portion of the interscapular space, near and over the bifurcation of the bronchi and also over consolidations in the lung.

In 1834, Beau (3) suggested that respiratory sounds are caused by the air passing through the glottis, the trachea, bronchi and alveoli, each producing its characteristic quality, the whole being transmitted as one sound to the surface of the lung. In normal chests the alveoli are supposed to dominate the picture, hence the name "vesicular murmur." In infiltrations bronchial elements are supposed to modify, causing "bronchovesicular" sounds; or dominate, causing bronchial sounds. Beau's suggestion of the cause of the sounds has determined our teaching for more than a century.

If the sounds are caused by the air rushing through the glottis and on into the finer air chambers, what causes the sound of expiration? Here the air is passing the other way. What causes the weakness of the murmur in abdominal as compared with costal breathing? The air rushes in—in the same volume and with similar speed. It enters the bronchi and the alveoli the same as in costal breathing. Why is it so weak in emphysema and rigid thorax? It still enters through the glottis.

An experiment is reported by Bondet and Chauveau (4) quoted by Powell and Hartley (5). A horse had pneumonia of the lower half of the left lung. "Exaggerated breathing was heard over the upper half of the left and the entire right

lung, while 'tubular' breathing was heard over the infected portion of the left lung." The trachea was then opened by an incision 20 centimeters long. The respiratory bruit was almost completely absent below the incision when held wide open. On auscultation over the consolidated portion of the lung no "tubular" sound could be heard on inspiration and only a faint sound on expiration. Over the remainder of the left lung and the entire uninfected right lung normal respiratory sounds were heard. They apparently accepted the idea of the sounds originating in the larynx, but concluded that the "pulmonary element takes an important share in the production of the normal respiratory sounds." While some of their findings seem contradictory, we must recognize that they suggested to the authors that there is a pulmonary element in the production of respiratory sounds.

It is necessary to bear in mind that these descriptions and suggestions were made by early observers who were working in a virgin field. Their experience in tuberculosis was probably confined to the far advanced. Their examinations were made at great disadvantage compared with to-day. The human chest was usually examined through clothing. Laennec said a bare chest was unnecessary. Structural pathology was undeveloped. The living pathology as we follow it now with the X-ray was decades in the future. The physiology of respiration was not understood. It was believed that air rushes from the glottis to the alveoli.

We have no evidence that anyone prior to Laennec had tried to describe or explain minutely what was heard on auscultation, although Greek physicians are reported to have listened to the lungs by placing their ears on the chest wall.

It is remarkable that Laennec could have given a description of the respiratory murmur and a classification of râles that should have endured for a century and a quarter. It is all the more remarkable when we recall that he died at the age of forty-five. Some of us have examined chests for fifty years and still are unable to clarify respiratory sounds to our full satisfaction.

Without belittling the opinions of these early workers it is time to add what we can, in the light of recent discovery, to make physical examination more inviting and more dependable.

Ornstein (6) has given careful study to the cause of the sounds and has come to the conclusion that they may be explained on the basis of physical laws and suggests that "the mechanism is similar to the production of a sound in a labial pipe," and that "the sounds are produced throughout the length of the bronchial tree wherever the intrushing column of air strikes the sharp edge of the bifurcating bronchus."

Sahli (7) observed a patient with congenital fissure of the sternum and reported that increased intraabdominal tension caused the lung to protrude and that the filling of the alveoli produced a murmur with vesicular qualities. The same has been found in inflating and deflating lungs removed from a cadaver.

I have taught for years that muscle sounds may simulate the respiratory murmur (8, 9, 10, 11, 12). If one listens over a contracting and relaxing muscle, for example the biceps, he may hear sounds similar to those over the chest, which

vary in pitch and intensity according to the tension in the muscles. A sound like a weak "respiratory" murmur may also be heard over the abdominal muscles below the costal margin, stronger in abdominal breathers.

Having found that sounds similar to the respiratory sounds can be heard over muscles in various phases of contraction; that a weak respiratory murmur often may be heard over the side of the chest in which a lung is partially collapsed and separated from the chest wall by air or fluid; that it is weak in high-grade emphysema where the intercostals are markedly distended and unable to function normally; and in rigid thorax where the muscles are functioning very little; I cannot but believe that we must change our opinion of the cause of respiratory sounds and assign them to a more complicated mechanism.

The air current, the bronchi, the alveoli, the lung mass, the respiratory muscles and the bony cage are all intimately involved in the respiratory act. That the larynx is limited as a factor is shown by the fact that the sounds are heard during bronchoscopy when the air enters through the tube, the same as in the experiment of Bondet and Chauveau, in which the air entered a wide incision in the trachea of a horse, as quoted above. The musculature of the bronchi which lengthens and dilates on inspiration and contracts and shortens on expiration undoubtedly influences the flow of the air and may cause some sound on its own part. The muscles of respiration, particularly the intercostals, are unquestionably important factors. The contraction of the crus and central tendon of the diaphragm and the abdominal muscles influences the murmur and enters into the sound directly. Size and form of the chest cavity, its elasticity, and the superficial muscles as well as those more intimately concerned with respiration, are all to be considered as factors.

Not only will careful auscultation show that the inspiratory murmur occupies the entire inspiratory phase whatever its length may be, but also that the expiratory murmur, while often weaker, occupies the expiratory phase. It will also show that the basic murmur qualitatively and quantitatively differs in different individuals and in different portions of the chest in the same individual. Pulmonary sounds, both normal and pathological, fail to conform to standardization.

Our premises are that respiratory sounds are expressed in vibrations set up by the entire respiratory mechanism. The vibrations are not limited to the column of air, nor the air plus the tubes through which it passes, nor these and the alveoli. They are wide-spread and involve the air column, the air passages, the pulmonary tissue, the muscles of respiration and bony thorax.

That muscles cause sound vibrations may be shown by placing the stethoscope over contracting muscles such as the biceps, or abdominal muscles below the costal border as mentioned above. Vibrations not unlike those heard over the lung are conducted to the ear during contraction and relaxation.

As the inspiratory muscles contract, the inrushing air itself vibrates. Moreover, vibrations are set up in the bronchi, alveoli and the superficial structures covering the chest. There is no doubt that the pressure of the air against the bronchial walls and in the alveoli, as suggested by Laennec, causes sound vibra-

tions. Moreover, there is no doubt that the air column, passing through the narrow glottis as suggested by Beau, is thrown into vibrations. It may be that the onrushing air striking the sharp edge of bifurcating bronchi causes sound similar to a "labial pipe" as suggested by Ornstein. But it seems to me that all these explanations are too limited. There is more to be considered than the air column.

When once we get a conception that the respiratory sounds are caused by all of the factors which form a part of the respiratory mechanism we will have a more rational approach to our problem. We will then understand that vibrations will continue throughout both the inspiratory and expiratory phases of respiration, and that the character of the sounds will be altered as the various factors in their production vary. We will then see that our findings on auscultation will be modified directly by our findings on inspection, palpation and percussion. The normal respiratory murmur is not a definite sound. Nor is the mechanism responsible for respiration a definite fixed quantity.

That the muscles are an important part of the respiratory murmur may be inferred, as above mentioned, by analyzing those conditions in which intercostal action is limited, such as emphysema; calcification and ankylosis of the costal cartilages which immobilize the bony cage; and breathing which is predominantly abdominal in character. In all these conditions the respiratory murmur is weak no matter if the same inrush of air enters the lung as in costal breathing.

A complete respiratory cycle consists of the inspiratory phase in which the diaphragm and external intercostals contract, the abdominal muscles relax, and the intrathoracic space is increased. The air rushes in and the elongated and dilated bronchi and the alveoli are filled. In the expiratory phase the diaphragm returns to its resting position as a result of the contraction of the abdominal muscles which increases the intraabdominal tension, and, with the aid of the internal intercostal muscles, restores the thoracic portion of the respiratory mechanism to its resting condition. During this last phase the air is expelled from the lungs, completing the cycle.

Active muscular effort takes part in both the inspiratory and expiratory phases of respiration. Respiratory vibrations continue throughout both phases, unless interfered with by some anomaly in the mechanism or by some pathological interference.

Pathological respiratory murmurs: An infiltrated area adds a hindrance or obstruction according to the degree to which the bronchi and alveoli are blocked and the elasticity of the pulmonary tissue is decreased. Infiltration interferes with both the ingress and egress of air. Air may not enter at all, or, if it does, it enters less easily. The respiratory movement is retarded. The lung expands more slowly and less completely than normal and takes longer to deflate. Part of this reduced movement of the chest wall is a muscular reflex and part of it is due to reduced expansion caused by the infiltration. The intercostal muscles prolong their inspiratory and expiratory action, and this influences the length and quality of the respiratory note.

In case of infiltration, it is evident that the sound vibrations in the air current,

the bronchial musculature, the alveoli, the bony thorax and the muscles of respiration may all be altered; but altered differently in different individuals and according to the nature of the infiltration.

So the effect of infiltration on the respiratory murmur is an impeding or lengthening of inspiration and slowing (prolongation) of expiration, probably raising the pitch somewhat and prolonging the phases because the air does not have the normal contractility of the alveolar tissues and bronchi to receive and expel it. Possibly an increased effort on the part of the respiratory muscles might be required, too. It is evident that the sounds would vary greatly with different types of infiltration and the different degrees of interference with the various factors which take part in the respiratory mechanism.

In limited infiltrations the variation may be so slight as to be imperceptible, while in extensive infiltrations it may be very marked. Different portions of the respiratory mechanism predominate at different times. The more complex the mechanism for causing respiratory sounds, the more will the sounds differ in different individuals even with the same morbid change. So, if the entire respiratory mechanism enters into the production of the respiratory murmur, we have a more reasonable explanation for the variation in sounds than we have if we consider only the changes in the current of air.

The blocking of a stem bronchus by a tuberculous lesion may allow very little air to enter the lung. This may diminish but I have not seen it obliterate the respiratory sound. The intercostal muscles still contract both on inspiration and expiration. If anything diminishes or increases the movement of a hemithorax, both inspiration and expiration may be weakened or exaggerated, prolonged or shortened according to the nature of the pathological change and the extent to which the movement is interfered with.

In emphysema the intercostal muscles, both external and internal, are stretched, and the intercostal spaces are widened and the action of the muscles is interfered with. The same is true in chronic asthma with addition of bronchial constriction. Under these conditions the muscular element is lessened and, while the patient may be able to breathe with fair ease when at rest (showing that the column of air enters the lungs), the respiratory sounds show degrees of weakness which now and then amount almost to inaudibility. The expiration is prolonged because of the inefficiency of the expiratory muscles and the overstretching of the pulmonary tissues and their lessened ability to contract. On extra effort the patient attempts to breathe fast but the muscles cannot respond. Every factor in the respiratory mechanism goes awry.

In certain patients with poliomyelitis in whom the intercostal muscles were involved, years after the attack I found the ribs horizontal, the intercostal spaces widened, the muscles distended and inefficient and the respiratory note prolonged and markedly diminished in intensity.

The rigid and emphysematous chests of the aged show a weak respiratory murmur, although there may be no recognized dyspnea.

Thus the column of air in emphysema, chronic asthma, the poliomyelitis chests above mentioned, rigid chests and abdominal breathers, enters the air

passages and penetrates the alveoli, but the vibrations set up are weak and the respiratory murmur is of low intensity. The muscular element is reduced in all these conditions.

An increased cellular and fluid content of the tissues, air cells and small bronchi, such as we see in pneumonia or the exudative type of tuberculosis (tuberculous pneumonia), may be accompanied by the usually described bronchial breathing. However, the transmission of the voice does not dominate the picture. On the other hand, in a preponderantly proliferative tuberculosis in which the fibrous elements predominate (scar tissue) the vibrations of the air column and tissues are high-pitched and prolonged and their transmission predominates over all other factors which cause respiratory vibrations.

A similar condition is met in case of cavitation. A cavity with soft walls in the midst of tissues which are infiltrated with inflammatory elements (the so-called silent cavity of Dunham) may not be detected by any characteristic respiratory sound. All the usual elements of the respiratory mechanism may contribute their vibrations but that of the voice and pulmonary tissues is not prominent.

On the other hand, a cavity with fibrous walls and open bronchus in the midst of dense fibrous tissue will transmit exaggerated air and tissue vibrations which produce a characteristic respiratory sound. If the mouth is held open and the syllables "ha ha" are repeated in a whisper and prolonged, a low-pitched blowing may be heard differing mainly in pitch from the sound heard over a dense scar without excavation.

The vibrations in the presence of extensive scar tissue, either with or without cavity, are predominantly of air column and tissue origin, the muscle element being overshadowed.

Adventitious sounds: Sounds which accompany respiration (râles or adventitious sounds) are of great diagnostic significance. They have borne the name "râles" since first described by Laennec. His division of *dry*, *moist* and *crepitant* râles is still followed and still supposed to designate the same conditions to which he assigned them one hundred and twenty-five years ago. We have not re-examined the respiratory sounds or the "râles" which often accompany them either in the light of more recent pathology or the findings of the X-ray.

One would get the idea from reading the literature of tuberculosis that râles are nearly always heard over tuberculous infiltrations. But such is not the case. Nor are all râles heard in a tuberculous chest of pulmonary origin. Many of them are extrapulmonary; and it is necessary to appreciate these as well as those of pulmonary origin.

All who are interested in râles should read the paper by Coplin (13) on the inflammatory and degenerative changes which take place in the pleura and intercostal tissues in diseases of the lungs and pleura. He gives a pathological basis for these adventitious sounds which are persistent after pleural involvement. I quoted from his paper extensively in *Clinical Tuberculosis* (11) and also in my forthcoming book on tuberculosis.

I have found clinically that râles may persist when the pleura has previously

been involved. They originate in both the pleura and the intercostal structures and usually are accompanied by an easily recognized degeneration of the overlying skin and subcutaneous tissue. These areas too are frequently the seat of recurrent and not infrequently of persistent pain.

That these râles are not of pulmonary origin may be inferred from the fact that they are frequently present when the X-ray film shows no abnormal pulmonary shadow. However, when they are present and the underlying pulmonary structure is also diseased, one cannot be so sure of the origin of the râles; they may arise either in the pulmonary or pleural tissues. Nevertheless, I have made it a rule to suspect, at least, a partial nonpulmonary origin if the overlying soft tissues are degenerated; for the trophic reflex in case of the pleura lies in the zones immediately overlying the inflamed area.

No doubt the cause of this degeneration is twofold: one reflex through injury of the intercostal nerves by long stimulation the same as in case of the trophic reflex in the cervical (particularly third, fourth and fifth) zones when the lung is chronically inflamed; the other is the direct effect of the chronic infection by continuity as suggested by Coplin.

I cannot emphasize too strongly the importance of recognizing the presence of these nonpulmonary râles. They cannot be differentiated by their sound or their size from the *subcrepitant* and the *crackling* râles which arise in the lung and which are usually described as being caused by mucus in the air passages.

It is usually taught that râles may be determined as being of pulmonary origin if they are detected following expiration, mild cough and prompt light inspiration. These nonpulmonary râles are heard following the same procedure. Nonpulmonary, usually designated as pleural râles, are supposed to be nearer the ear, but differentiating the location of râles within a distance of a centimeter or two, to say the least, is uncertain.

Of course, the whistling and gurgling, the rhonchi and wheezes, are a different story. They are definitely of pulmonary and bronchial origin.

DISCUSSION

With the inaccuracy in description of the normal respiratory murmur, the probably wrong explanation of the mechanism of its production and the inaccuracy of our knowledge of râles, is it any wonder that there should be confusion on the part of clinicians in interpreting the data obtained on auscultation? That physicians examine better than their teaching would warrant, goes without saying; for each learns certain sounds and certain modifications of them which he interprets in a certain manner.

Another important fact must be understood. No type of murmur or modification of that type always means the same pathological change. We would like to think that whenever a pneumonia is present a given sound will be found; and that, whenever we find that sound, pneumonia will be present. We would like the same for the various pathological changes found in tuberculosis, lung abscess, bronchitis, bronchiectasis and so on. But it is not true.

If all lungs were of the same volume and had the same degree of elasticity;

all bony thoraces were equally elastic or rigid; all musculature of equal volume and tension; all larynges were of equal capacity; all pleurae and mediastina were free; and the respiratory demands were the same on each individual, then the normal respiratory murmurs could be described as fixed and definite, and a given departure might mean a definite pathological alteration. But since these things are not true, each clinician must learn that variability is the rule in both normal and pathological chests.

Moreover, it must always be remembered that pressure on the stethoscope decreases the intensity of respiratory sounds and that the fundamental characteristic of tones heard varies with different stethoscopes according to the size and nature of the bell and the character of the rubber tubes used. In teaching respiratory sounds, teacher and student should use the same kind of stethoscope if they would speak the same language, or one bell with multiple ear pieces.

Any good diagnostician has doubtless been confused on auscultating chests by finding sounds which he was not able to interpret according to the descriptions found in the books. He may find the so-called vesicular murmur over a cavity and bronchial respiration over apparently normal pulmonary tissue and absent over infiltrations where he has learned it should be. He frequently will find râles that he has been taught to consider as belonging to a tuberculous infiltration where other signs fail to show such lesions. Yet if he will carefully inspect, palpate, percuss and auscultate, and as carefully analyze the phenomena discovered, he will find that even without an X-ray examination he is able to determine pulmonary and pleural lesions with great accuracy.

If the respiratory sounds are the product of vibrations originating in all parts of the respiratory mechanism, it is all the more necessary to interpret the knowledge gained on auscultation in accordance with that obtained by other methods of physical examination. So it is important to recall the data which may be derived by inspection, palpation and percussion and discuss briefly how this may affect the respiratory mechanism.

Inspection: Aside from giving the examiner a general idea of the patient and acquainting him with any deformities or gross departures from the normal, careful inspection will provide valuable information of what is going on within the chest at the time of the examination and what has transpired previously that may modify the respiratory murmur. In combination with palpation, inspection will reveal reflex spasm and atrophies which indicate both present and past disease and cause the examiner to suspect changes in the respiratory murmur.

Palpation: Textbooks teach that by palpation one can note such things as the texture of the skin, the presence or absence of enlarged lymph nodes, and the vibrations caused by the spoken voice. But these are least important from a diagnostic standpoint of all the things that may be detected by palpation.

Increased tension of the apical muscles is important confirmatory evidence when an active tuberculosis is present in the underlying lung. Degeneration of the same muscles and the skin and subcutaneous tissue above the second rib anteriorly and the spine of the scapula posteriorly is evidence that the lung

is the seat of a chronic or healed lesion usually tuberculosis. These are important diagnostic data, and a knowledge of their presence is necessary to the proper interpretation of auscultatory findings. Likewise, the boardiness of the intercostal muscles immediately over an acute pleurisy, and the degeneration of the skin, subcutaneous tissue and intercostal muscles when the pleurisy persists for any length of time are of great diagnostic value and indicate probable changes in the respiratory sounds. This degeneration may be found anywhere between the second rib anteriorly and the spine of the scapula posteriorly above, and the margin of the ribs below.

In chronic or healed pleurisy adventitious sounds are heard frequently and sometimes persistently over these same areas that show degeneration of the intercostal muscles and overlying subcutaneous tissues. These râles are sometimes heard without coughing but oftener when the patient gives two or three easy coughs and follows with a short quick inspiration. The roentgenogram may show nothing at all, but the effects of the former changes in the pleura and intercostal tissues may be clearly seen in the atrophied superficial tissues. In this connection it must be stated that râles are not always present even though the degeneration of tissues shows that pleurisy was formerly present. However, some degree of lessened motion is usually present. Many times pain is felt in these areas under conditions of stress such as tiring, emotional upsets, menstruation and change in weather. This pain is due to injury of the intercostal nerves as a result of the chronic inflammation. Understanding the origin of this trophic reflex and pain is essential to the interpretation of the respiratory sounds heard under these circumstances.

Lagging and lessened motion of the chest wall in some particular area or on one side, or as a whole, is of great diagnostic significance. Of importance, too, is the detection of different degrees of density in the tissues according to the underlying pathological changes noted on palpation.

It is important to know that infiltrations and emphysema, and fluid and air in the pleura, can be determined by palpation as well as percussion, and that these alter the percussion note.

The data obtained on palpation have bearing on the auscultatory sounds in proportion to the degree that they cause changes in the respiratory mechanism.

Percussion: Physicians learn to recognize differences in quality, intensity and pitch of the percussion note. Their fingers are trained to perceive different degrees of resistance over percussed areas. Many depend far more on the sensation conveyed to the fingers than on the sound elicited; and many of our best diagnosticians pay little or no attention to sound but learn to percuss almost without producing sound. This is only one step removed from detecting different degrees of density by palpation. The data derived by percussion, the same as by palpation, suggest an alteration in the respiratory note to the extent that they interfere with the respiratory mechanism.

This discussion may at first seem to take away the whole basis on which auscultation stands. Instead, more careful study will show that it only broadens

the base and furnishes an explanation for the difficulties and inaccuracies which have heretofore confused the clinician. *By suggesting auscultation as being a method of studying the whole respiratory mechanism instead of the air current, it gives a better conception of what is going on within the respiratory system.*

SUMMARY

1. The long taught description of the relative length of inspiratory and expiratory breath sounds is erroneous. They are about equal in length—inspiration occupying the entire inspiratory phase and expiration occupying the entire expiratory phase.

2. The suggestions that the respiratory murmur is caused by air pressing against the walls of the bronchi, dilating and closing the alveoli as suggested by Laennec, by passing through the glottis as suggested by Beau, or by striking the sharp edges of the bifurcating bronchi as suggested by Ornstein, simplify the respiratory murmur too much. While all may be factors they are not the whole cause. The cause is very complex and includes vibrations in all parts of the respiratory mechanism. Inspiration is caused by contraction of the external intercostal muscles and diaphragm, enlarging the chest cavity and causing the lung to expand, the bronchi to dilate and lengthen, and the alveoli to open. Expiration is caused by the contraction of the abdominal and internal intercostal muscles, and relaxing and restoring the diaphragm to its resting position, diminishing the size of the thoracic cavity and allowing the lung to return to its normal resting size, shortening and lessening the lumen of the bronchi and relaxing the alveoli.

3. Râles are both pulmonary and extrapulmonary. The latter may be caused by a chronic pleuritis extending to the intercostal structures, or to reflex trophic effects in the same structures.

4. There is no definite sound that denotes a definite disease. The respiratory mechanism would always have to be the same to make the respiratory note always the same.

SUMARIO

La Auscultación—Una Re-Avaluación

1. La vieja descripción de la relativa duración de las fases inspiratoria y expiratoria de los ruidos respiratorios peca de errónea. Su duración es aproximadamente igual, ocupando la inspiración toda la fase inspiratoria y la expiración toda la expiratoria.

2. Las sugerencias de que el soplo respiratorio es producido por el aire, que al comprimir las paredes de los bronquios, dilata y cierra los alveolos, según insinuara Laennec, o al atravesar la glotis, según Beau, o al herir los agudos bordes de las bifurcaciones bronquiales, según Ornstein, simplifican demasiado el soplo respiratorio. Aunque todos esos fenómenos pueden ser factores, no constituyen toda la causa. Esta es muy compleja y comprende las vibraciones de todas las partes del mecanismo respiratorio. La inspiración tiene por causa la

contracción de los músculos intercostales externos y del diafragma que dilata la cavidad torácica y hace que el pulmón se expanda, que los bronquios se dilaten y alarguen y que los alveolos se abran. La expiración se debe a la contracción de los músculos intercostales abdominales e internos y a la dilatación y restablecimiento del diafragma en su posición de reposo, y la disminución del tamaño de la cavidad torácica, que al dejar que el pulmón recupere su tamaño normal en descanso, acorta y achica la luz de los bronquios y dilata los alveolos.

3. Los estertores son tanto pulmonares como extrapulmonares, pudiendo deberse los últimos a una pleuritis crónica que se extiende a los tejidos intercostales, o a efectos tróficos reflejos sobre los mismos.

4. No existe ningún ruido bien definido que denote una enfermedad bien definida. El mecanismo respiratorio tendría que ser siempre el mismo para producir una nota respiratoria siempre idéntica.

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THE HEALTH CARD AND THE ABREU METHOD

Their Use in Asuncion, Paraguay

ANGEL R. GINES¹

In July, 1941, we started the organization of the Prophylaxis Section of our Tuberculosis Dispensary. By a thorough newspaper campaign we were able to start our task by examining the close relatives of consumptive persons, others who came to us on their own free will in a somewhat irregular manner, and the staffs of some public firms and private concerns, whose heads realized the importance of the work we proposed to carry out. In November, 1941, the Ministry of Public Health realized the possibility of making a collective examination. It amplified a law of 1938, enforcing the use of the Health Card, which made X-ray examination of the lungs obligatory for all public officials, public and private employees, teachers, students, and professional persons, as well as of those people who are about to travel.

Up to the time of writing this report we have taken X-ray photographs of 120,000 persons (1941-1946). The examinations consist of a tuberculin test, an X-ray photograph of the lungs and a brief examination of the skin and mucous membranes. Occasionally, and always with an investigative point of view in mind, biotypological data are taken, such as complexion, height, weight, chest circumference, etc. Since 1945 we have also paid attention to the physical examination of the abdomen. BCG vaccination is given to all those persons who are tuberculin-negative.

We can examine 200 persons in three hours with ease and the results of these examinations are delivered forty-eight hours later. In this lapse of time, it is possible to examine the X-ray photographs which were taken and to fill in the Health Card to be handed to the examined persons. When abnormalities of the heart and main arteries are found, or if it is necessary to carry out a further examination within a certain time, the facts are entered in the respective cards. Any suspicious lesion of the lungs is checked and X-rayed to make an accurate diagnosis. In such cases, the laboratories are instructed to take a blood count, blood sedimentation rate, and to examine the sputum.

Studies of the gastric contents are rarely carried out. Instead we have introduced bronchial lavage according to the method of Abreu and R. Fernandez. In this technique, the posterior pharynx is anesthetized with 0.1 per cent pantocaine, usually administered by atomizer. The tongue is pulled forward and about 10 cc. of saline is quickly injected into the posterior pharynx above the epiglottis. The ejected material is collected and examined for tubercle bacilli. We consider this procedure practicable since it can be done at any time.

Persons suffering from heart disease are urged to place themselves in the hands of private practitioners or of the public dispensaries. People suffering from

¹ Professor of Internal Medicine, Director of the Health Institute Control for Individuals and Communities, Head of the Prophylaxis and Epidemic Section of the Asuncion Tuberculosis Department, Asuncion, Paraguay.

lung disease are notified that they should report to the Tuberculosis Dispensary or at a hospital for treatment. When the patient is a worker or an employee of a

TABLE 1
Apparently well persons of each sex who were X-rayed each year, classified by age group: Asuncion, Paraguay, 1941-1944

AGE GROUP	1941-1944 (TOTAL)			1944		1943		1942		1941	
	Both sexes	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
All ages.....	73,704	46,330	27,374	13,614	7,833	14,952	8,644	13,060	6,867	4,704	4,030
Under 3 years.....	173	82	91	29	25	15	16	14	11	24	39
3-5 years.....	357	172	185	61	70	52	44	21	24	38	47
6-10 years.....	1,842	733	1,109	125	194	345	449	82	136	181	330
11-15 years.....	7,718	4,137	3,581	1,324	973	1,654	1,231	857	671	302	706
16-20 years.....	14,258	7,869	6,389	2,557	1,919	2,601	1,964	2,003	1,696	708	810
21-30 years.....	22,911	14,173	8,738	4,267	2,493	4,253	2,619	4,200	2,496	1,453	1,130
31-40 years.....	13,570	9,562	4,008	2,677	1,196	2,962	1,236	2,915	1,031	1,008	545
41-50 years.....	7,205	5,158	2,047	1,347	598	1,655	663	1,604	528	552	258
51-60 years.....	4,198	3,265	933	883	264	1,045	324	996	216	341	129
61 years and over ...	1,472	1,179	293	344	101	370	98	368	58	97	36

TABLE 2
Percentage of primary infections found among apparently well persons of each sex who were X-rayed each year, classified by age group: Asuncion, Paraguay, 1941-1944

AGE GROUP	PERCENTAGE OF PRIMARY INFECTIONS FOUND							
	1944		1943		1942		1941	
	Male	Female	Male	Female	Male	Female	Male	Female
All ages.....	1.3	1.1	0.7	0.7	0.6	1.0	0.9	1.3
Under 3 years.....	1	—	1	1	1	1	1	1
3-5 years.....	1	1	1	1	1	1	1	1
6-10 years.....	8.8	3.1	4.6	3.8	1	1	1	1
11-15 years.....	1.8	2.1	1.9	1.3	1.6	2.5	1.0	4.2
16-20 years.....	1.4	1.0	1.1	0.4	0.7	0.5	1.6	1.4
21-30 years.....	1.1	0.9	0.5	0.4	0.5	0.4	0.8	0.4
31-40 years.....	1.0	0.6	0.2	0.2	0.4	0.5	0.2	0.9
41-50 years.....	0.9	1.3	0.1	0.2	0.2	—	—	—
51-60 years.....	0.7	0.4	—	—	0.4	0.9	0.3	—
61 years and over.....	—	—	—	—	—	—	—	—

¹ Per cent not shown when base is less than 100.

private company and he is found to have tuberculosis, the Social Insurance Division is notified for the necessary follow-up examinations. The persons with syphilis are sent to the respective institutions for treatment. (In the finding of

TABLE 3

Percentage of minimal lesions found among apparently well persons of each sex who were X-rayed each year, classified by age group: Asuncion, Paraguay, 1941-1944

AGE GROUP	PERCENTAGE OF MINIMAL LESIONS FOUND							
	1944		1943		1942		1941	
	Male	Female	Male	Female	Male	Female	Male	Female
All ages.....	0.3	0.3	0.4	0.3	0.6	0.3	0.4	0.2
Under 3 years.....	—	1	—	—	—	—	—	—
3-5 years.....	—	—	1	—	—	—	—	—
6-10 years.....	—	—	—	—	—	—	0.6	—
11-15 years.....	0.1	0.1	0.3	0.3	0.4	—	0.3	—
16-20 years.....	0.2	0.1	0.5	0.3	0.3	0.3	0.6	0.5
21-30 years.....	0.3	0.2	0.4	0.3	0.8	0.3	0.3	0.2
31-40 years.....	0.4	0.6	0.4	0.3	0.3	0.5	0.5	—
41-50 years.....	0.3	0.7	0.2	—	0.5	0.2	0.7	0.4
51-60 years.....	0.3	—	0.6	0.6	0.9	0.5	—	0.8
61 years and over.....	2.0	1.0	—	—	0.5	—	—	—

¹ Per cent not shown when base is less than 100.

TABLE 4

Percentage of gross lesions found among apparently well persons of each sex who were X-rayed each year, classified by age group: Asuncion, Paraguay, 1941-1944

AGE GROUP	PERCENTAGE OF GROSS LESIONS FOUND							
	1944		1943		1942		1941	
	Male	Female	Male	Female	Male	Female	Male	Female
All ages.....	0.8	0.5	0.9	0.8	1.2	0.8	1.7	1.1
Under 3 years.....	—	—	—	—	—	1	—	—
3-5 years.....	—	—	—	—	—	—	—	—
6-10 years.....	—	—	0.3	—	1	—	1.1	0.3
11-15 years.....	0.2	0.1	0.2	0.3	0.4	0.2	0.7	—
16-20 years.....	0.2	0.2	0.6	0.4	0.4	0.5	0.6	1.1
21-30 years.....	0.7	0.7	0.9	1.1	1.2	0.7	1.6	1.7
31-40 years.....	1.3	0.6	0.8	0.6	1.2	1.3	2.2	1.8
41-50 years.....	1.5	0.7	1.2	1.2	1.9	1.1	2.5	0.4
51-60 years.....	1.7	1.1	2.5	2.2	2.1	2.8	2.1	1.6
61 years and over.....	3.2	1.0	3.5	1	2.7	1	1	1

¹ Per cent not shown when base is less than 100.

syphilis, the Chediack microreaction is used.) Patients with leprosy are compelled to be interned in the Leprocomium at Sapucay, some fifty miles from Asuncion.

The results of our research have been presented in different publications.

TABLE 5*
Percentage of males and females who had positive reactions to tuberculin tests, classified by age group: Asuncion, Paraguay, 1941-1948

AGE GROUP	PERCENTAGE OF POSITIVE REACTIONS FOUND					
	1943		1942		1941	
	Male	Female	Male	Female	Male	Female
	93	90	96	94	98	96
All ages.....	—	1	—	—	1	1
Under 3 years.....	—	1	—	—	1	1
3-5 years.....	1	1	1	1	1	1
6-10 years.....	68	88	90	76	72	95
11-15 years.....	88	86	95	94	95	92
16-20 years.....	90	88	95	95	95	96
21-30 years.....	96	94	97	96	96	98
31-40 years.....	99	96	97	97	99	98
41-50 years.....	99	98	97	94	100	99
51-60 years.....	99	99	99	100	100	100
61 years and over.....	99	1	99	1	1	1

* Per cent not shown when base is less than 100.

* BCG vaccination was introduced in Paraguay in August, 1941 by our Institute. From that date on to October, 1944, 1,052 infants and 1,336 children and adults were vaccinated by the method of Rosenthal.

In order to get information concerning the value of BCG vaccination, approximately one-half of the tuberculin-negative reactors were vaccinated (in alternate weeks). The other half served as a control group. After four years of working on this subject we learned that the control group presented a morbidity of 9 per cent (5 per cent pulmonary lesions and 4 per cent hilar or mediastinal lymphadenopathy), while the vaccinated group revealed an incidence of 1 per cent of hilar lymph node and no pulmonary lesions.

After this experience BCG vaccination was performed on all tuberculin-negative reactors without limitation of age.

SUMMARY

A Health Institute for Individuals and Communities has been established in Asuncion to provide health cards to all persons who carry out their part in the communal activities by means of their trade or profession. In order to obtain the health card, each person pays Gs.2 (60 cents) and undergoes an X-ray examination, a chest examination, a tuberculin test and examination of the skin and mucous membranes. BCG vaccination is given to the negative tuberculin reactors.

Through these examinations we screen out patients with pulmonary, cardiac and venereal diseases and those with leprosy. The card is not issued to people with contagious diseases, such as tuberculosis, syphilis in its contagious stage, leprosy etc. In this way many people have learned for the first time that they were victims of such diseases and have promptly been treated for their respective ailments. This quick intervention and the consequent control that we exercise

over the patients have allowed them to avoid what might eventually have led to irreparable damage to their health.

The Abreu method which is used is perhaps rather more expensive than fluoroscopy but has proved to be highly superior in the number of pulmonary cases it has brought to light.

SUMARIO

En Asunción han establecido un Instituto para el Control de la Salud en los Individuos y Colectividades que expide carnets de salud a todas las personas cuyo oficio o profesión las ponen en contacto con el público general. A fin de obtener el carnet cada persona paga dos guaraníes (aproximadamente 60 centavos m/a) y es objeto de un examen radiográfico, un examen del tórax, una prueba con tuberculina y un examen de la piel y mucosas. A los negativos a la tuberculina se les vacuna con BCG.

Esos exámenes permiten separar a los enfermos con afecciones pulmonares, cardíacas y venéreas y con lepra, sin que se expidan carnets a los que padecen de dolencias contagiosas; por ej., tuberculosis, sífilis en el periodo contagioso, lepra, etc. En esta forma muchos han averiguado por primera vez que eran víctimas de tales males y se han hecho tratar sin tardanza. La rápida intervención con la consiguiente vigilancia ejercida sobre los enfermos les permite evitar lo que con el tiempo hubiera podido acarrear lesiones irreparables a su salud.

La técnica de Abreu, que es la utilizada, tal vez resulte más costosa que la roentgenoscopia, pero ha resultado ser muy superior en lo referente al número de casos pulmonares puestos de manifiesto.

BRITISH COLUMBIA'S WELFARE PROGRAM FOR THE TUBERCULOUS

HELEN M. SUTHERLAND¹

British Columbia is the most western of Canada's nine Provinces and it is also the most progressive in matters of social legislation. The development of both public and private agencies has been unhampered by the dead-weight of the traditional way of doing things that has retarded progress in other parts of the country.

This freedom to seek new ways of dealing with the needs of the people of the Province has been most evident in the development of a public welfare program for those who require financial help or case-work services anywhere in the Province. Large areas of the Province are "unorganized," that is, there is no municipal or local government, and the administration of such matters as taxes, law enforcement and social services is the direct responsibility of the Provincial Government.

The Department of Health and Welfare has a Social Welfare Branch which is concerned with all the needs of the people including problems of child welfare, pensions for the aged, case-work services in Provincial institutions such as mental hospitals, tuberculosis sanatoria and industrial schools, financial assistance and family case-work services. Trained social workers are stationed in district offices throughout the Province giving a generalized service. They report to the appropriate Division concerned, such as the Child Welfare Division or Tuberculosis Division, when matters of policy or administration are concerned, but the responsibility for the quality of the work done rests with the local worker and with the case-work supervisors in the district and regional offices.

In the areas which are organized into municipalities or cities, the municipality may provide its own social services, as the larger cities do, or they may turn to the Provincial Government for aid in providing adequate services to their residents. In addition to this form of assistance, the Provincial Government has undertaken to reimburse the municipalities 80 per cent of the cost of the financial aid given in the form of direct assistance, if the municipality meets the standards of the Provincial Department in the amount of assistance granted and the method of granting it. If a recipient is a resident of a Provincial area, the Provincial Government bears 100 per cent of the cost.

Social Allowances replaced the old form of Unemployment Relief in 1942. To be eligible for a Social Allowance a person must have been a resident of the Province for twelve months without receiving public assistance. He must be unemployed by reason of physical condition, family responsibilities or, in certain cases, by reason of age. For general purposes a woman of 60 or a man of 65 is considered unemployable. An applicant may possess personal property,

¹ Provincial Supervisor, Tuberculosis Social Service, 2647 Willow Street, Vancouver, B. C.

in addition to the necessary household equipment and wearing apparel, in the amount of \$250 if single without dependents, or \$500 if married or with dependents. Savings or capital over this amount must be expended for maintenance. A dependent child over 16 years of age must be regularly attending some form of educational institution such as an academic, technical or vocational school, and must be making satisfactory progress if he is physically and mentally able to maintain himself otherwise.

In 1944 the Social Welfare Branch and the Director of Welfare recognized that tuberculosis was a chronic illness with special requirements in the way of adequate diet and better housing. In order to prevent a patient's breaking down again after he had benefited by treatment and to minimize the economic factor in the planning of treatment, extra allowances to tuberculosis patients were authorized. As in the basic social allowance, 80 per cent of the cost in municipal cases and 100 per cent in Provincial cases was borne by the Provincial Government. There is a difference in eligibility, however, which is of great advantage in dealing with patients newly diagnosed as having tuberculosis. As soon as a diagnosis is made, if a patient, who would be eligible on other counts to get a Social Allowance, has to give up his job, he may apply immediately for assistance. If he has savings or capital over and above the \$250 or \$500 allowed in the other cases, he does not have to expend it for maintenance, but may keep it. However, an interest rate of 3 per cent is considered to be income, and this amount is deducted from the Basic Allowance. This leeway in the matter of savings has made it much less difficult to persuade people to give up their jobs and apply for assistance, when they know that the efforts of a lifetime of saving do not have to be spent merely to keep alive.

In addition to the difference in eligibility, the amounts allowed tuberculosis patients are larger. The patient himself is entitled to \$7.50 a month extra diet allowance as long as he is in his home. When he goes to the sanatorium his share of the allowance, including extras, is cut off but is reinstated immediately when he returns home. In order to protect, as far as possible, members of a patient's family who have been in contact with the disease, an extra diet allowance of \$5 a month each is granted on the recommendation of a doctor employed by the Division of Tuberculosis Control. When no medical need exists for the protection of these contacts this part of the allowance may be cancelled. The portion of the Basic Allowance supposed to be spent on rent is not adequate in these days of housing shortages and many of our patients have been living in totally inadequate quarters. To remedy this, in so far as possible, a rent differential is granted. The patient is given in cash the difference between the Basic Rent Allowance and the actual rent paid. In addition to these two extra allowances there are discretionary allowances which may be granted on the recommendation of the social worker dealing with the family. These may be mortgage payments, installment payments on property or necessary furniture, or insurance premiums where the policy cannot carry itself.

Beside the allowances granted the patient while he is at home, a monthly allowance of \$3.00, called a Comfort Allowance, is granted to him while he is in

HELEN M. SUTHERLAND

the sanatorium, general hospital awaiting sanatorium placement or in a supervised boarding home. Certain other patients who have not received Social Allowance, but who are classed as border-line cases, having no assets or funds to be used in the purchase of such things as stamps, hair cuts etc., may also be granted \$3.00 Comfort Allowance.

A Mothers' Allowance Act sets out the eligibility requirements in families where the father is totally disabled for a period of one year, so that the amount of capital allowed a family granted Mothers' Allowance because of tuberculosis is much smaller than in other cases of Social Allowance. In all other respects, such as extra diet allowance, rent differential and discretionary allowances, families receiving Mothers' Allowance are given the same extra financial assistance as Social Allowance families are.

Although this form of extra allowances has been in force for two years, we have so far no accurate statistics as to its effect on the number of patients in whom further breakdown was prevented, or for whom readmissions have not been necessary. However, in considering individual cases, we are well aware of the difference that these small sums have made in the peace of mind of patients who are facing a difficult enough time when they are told that they have tuberculosis. The feeling that they are given special consideration, and that everything possible is done to make it easier for them to get the allowance, has made it possible for many patients to give up their jobs and come into the hospital sooner than they would have done under the old system. A man who has managed to save several hundred dollars which he has put into Victory Bonds and earmarked for the education of his children feels that he is depriving them if he has to use that money for maintenance. Therefore, the waiving of the eligibility rule requiring patients to be practically destitute has been particularly beneficial.

SUMMARY

In the Province of British Columbia a family receiving Social Allowance because of tuberculosis has had extra consideration since 1944. Capital or savings do not have to be spent for maintenance, as an allowance will be granted when a patient's income ceases. The basic allowance is supplemented by \$7.50 a month extra diet allowance for the patient and \$5.00 a month extra diet allowance for each member of the patient's family who has been exposed to tuberculosis. Rent differential may be granted in cases where it is necessary, and discretionary allowances covering installment payments on essential furniture, mortgage payments, insurance premiums, etc. may be granted at the discretion of the Director of Welfare. Similar extra allowances are available to families receiving Mothers' Allowance instead of Social Allowance.

SUMARIO

Las Obras pro Tuberculosos de la Columbia Británica
En la provincia de Columbia Británica en el Canadá toda familia que recibe Subsidio Social por tuberculosis goza de nuevos beneficios desde 1944, y no tendrá

que gastar su capital o ahorros en manutención, pues se le concederá una pensión cuando cesen las entradas del enfermo. El subsidio básico es complementado con una pensión para alimentos que representa 7.50 dólares mensuales para el enfermo y 5 dólares mensuales para cada familiar expuesto a la tuberculosis. Si es necesario, puede concederse un subsidio para alquiler de vivienda, e igualmente subsidios para muebles indispensables, pagos de hipotecas, primas de seguros, etc., a discreción del Director de Beneficencia. Hay subsidios semejantes para las familias que reciben Subsidios Maternales en vez de Subsidios Sociales.

PULMONARY TUBERCULOSIS IN CHINESE STUDENTS

J. C. TAO¹

During the period of May, 1944 to March, 1946, 17,155 students from various high-schools and universities in Chungking were fluoroscopically examined. Among this group, 13,327 were boys and 3,828 were girls. The age varied from 10 to 36. No primary school children were included in this survey because, from the public health point of view, the detection of a single case of tuberculosis among 100 10-year-old children would not be justified for the same expenditure as that incurred in the examination of an equal number of 20-year-old students with the detection of 6 or 7 cases of disease.

PROCEDURE

Consent of the school health authority was obtained before examination of each school, so the examination was more or less compulsory. Therefore, the attendance of students in this survey covered more than 90 per cent of the school population and the results are considered significant from an epidemiological point of view.

During examination, all males were stripped to the waist and females were allowed to wear a single underwear. The examiner wears a pair of colored goggles for ten minutes before examination so that his pupils are well accommodated. Then the chest of the subject is systematically examined. Diaphragmatic shutters are used for close scrutiny. Rotation through 45° to both sides is a very useful procedure for the detection of lesions hidden behind radio-opaque structures. All cases with suspicious shadows on the screen are reexamined after a short interval and then roentgenographically. This check-up examination after two weeks is important to rule out the possibility of nonspecific pneumonitis. When erythrocyte sedimentation rate and sputum examination are done step by step. Special inquiry is made into family and contact histories with known tuberculous patients. Cases with questionable activity are asked to have follow-up examinations at one to three months' intervals.

RESULT OF EXAMINATION

Among the 17,155 students examined, 1,184 (6.9 per cent) were found to have active pulmonary tuberculosis. Lesions with questionable activity and small infiltrations appearing as sharply defined strands or spots at the extreme apex with salient-shaped projections of irregularly thickened pleura are not included in the statistics. Therefore, all the cases found are clinically significant. The Diagnostic Standards of the National Tuberculosis Association of the United States are closely observed in classifying these lesions. Table 1 shows the percentage of active pulmonary tuberculosis among students

¹ National Institute of Health, 1 Hwang-pu Lu, Nanking, China.

TABLE 1

Prevalence of active pulmonary tuberculosis among 17,155 students of different schools in Chungking

SCHOOL	NUMBER OF STUDENTS EXAMINED		NUMBER OF CASES FOUND		PERCENTAGE OF CASES FOUND	
	Male	Female	Male	Female	Male	Female
National Central University.....	3,669	755	299	47	8.1	6.2
Central Institute of Political Sciences	1,657	50	118	4	7.1	—
National Chungking University.....	1,147	237	127	6	11.0	2.5
Central Institute of Technology.....	1,034	24	104	1	10.0	—
National College of Fine Arts.....	197	70	13	4	6.6	—
National Yale Medical College.....	118	129	7	5	5.9	3.8
Provincial College of Education.....	139	61	21	5	15.1	8.1
Army Munition School.....	181	—	12	—	6.6	—
Army Accounting School.....	49	—	6	—	—	—
Total.....	8,191	1,326	707	72	8.1	5.4
*Nankai High-School.....	1,828	936	72	21	3.9	2.2
*Shujen Junior High-School.....	550	304	17	7	3.1	2.3
National Central High-School.....	344	201	20	9	5.8	4.4
*Isinhua High-School.....	399	124	18	5	4.5	4.0
Provincial Vocational School for Girls	—	441	—	34	—	7.7
Chungking High-School.....	352	—	14	—	4.0	—
Municipal High-School.....	340	—	24	—	7.0	—
Paper Manufacturing School.....	309	12	22	1	7.1	—
Psychological Experimental Class						
National Central University.....	71	12	1	0	—	—
*Yuyin Junior High-School.....	73	38	3	1	—	—
Total.....	4,266	2,068	191	78	4.5	3.8
Training Classes, N.I.H.....	15	112	3	10	—	8.9
Volunteer Students, Educated Youth						
Volunteer Corps.....	560	263	40	17	7.1	6.5
†Other Schools.....	295	59	55	11	18.7	—
Grand total.....	13,327	3,828	996	188	7.5	4.9
<i>Summary</i>						
Private.....	2,850	1,402	110	34	3.9	2.4
Public.....	1,416	666	8.1	44	5.7	6.6

* Private schools.

† Suspected cases included.

Among the high-school children, 4,252 belong to private schools, while 2,082 belong to public schools. This shows that the economic factors of the students have a great influence on the morbidity rate of tuberculosis. The reason why female students show much greater differences might be explained by the fact that girls have less chance of being infected, but when they do get infected they get a good stiff dose and easily die of it.

There is no question that age is the most important factor influencing the tuberculosis morbidity. Age specific morbidity is shown in table 2.

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in different schools. Schools with stars are private while the rest are public. All colleges and universities belong to the latter class. From the table it can be clearly seen that college students have a higher rate than students of high-schools. Table 2 shows that below 16 the two sexes have about the same prevalence of active pulmonary tuberculosis, while above 16 both sexes have a gradual increase of the percentage of active cases. The rate of increase is much more rapid in

TABLE 2
Prevalence by age groups of active pulmonary lesions of adult type

AGE GROUPS IN YEARS	NUMBER EXAMINED		NUMBER OF CASES		PERCENTAGE OF CASES	
	Male	Female	Male	Female	Male	Female
10-12	372	192	11	7	2.9	3.6
13-14	1,158	546	24	9	2.3	1.7
15-16	1,208	617	52	28	4.3	4.5
17-18	1,809	643	110	29	6.1	4.5
19-20	2,439	802	185	43	7.6	5.4
21-22	2,581	494	215	31	8.3	6.3
23-24	2,259	287	215	21	9.5	7.3
25-26	1,020	111	114	10	11.1	9.0
27-36	342	58	51	7	11.5	—
Unknown	139	78	19	3	—	—
Total.....	13,327	3,828	996	188	7.5	4.9

TABLE 3
Classification of cases of pulmonary tuberculosis found

TABLE 3					188	7.5	4.9
<i>Classification of cases of pulmonary tuberculosis found</i>							
SEX	MINIMAL	MODERATELY ADVANCED	FAR ADVANCED	TOTAL			
Male.....	694 (69.7%)	280 (28.1%)	22 (2.2%)	996			
Female.....	147 (78.2%)	38 (20.2%)	3 (1.6%)	188			
Total.....	841 (71.0%)	318 (26.9%)	25 (2.1%)	1,184			

males. This phenomenon might be explained on the basis of high-school, pupils have more contact with infected. Girls are not as active with sources of infection.

males. This phenomenon might be explained on the basis that, after entering high-school, pupils have more contact with society and so more chances of being infected. Girls are not as active as boys, and so have less chance of contacts with sources of infection. Among the cases found, 71 per cent are minimal. (See table 3.) Among these cases found more than 80 per cent are asymptomatic and cannot be diagnosed without such survey examinations.

COMMENT

The importance of early diagnoses of pulmonary tuberculosis has been repeatedly emphasized. Ordinarily, even when first symptoms are noted, a majority of cases are found to have moderately advanced or far advanced disease, for

tuberculous lesions commonly progress to these stages before causing definite symptoms. It is now widely recognized that before the onset of symptoms there is a period of months or even years during which the lesion can be detected by X-ray examination only.

The prevalence of early pulmonary tuberculosis is equally high among healthy robust students and those who look delicate or pale. Selection for examination on the basis of underweight, pallor, anorexia is without value in detecting early tuberculosis. Physical examination has no significance in the early detection of pulmonary tuberculosis either, because restriction to those with abnormal physical findings reveals almost the same prevalence of asymptomatic tuberculous lesions as that found in the apparently healthy group. On the other hand, definite harm is done by the physical examination when no abnormal signs are found, because it gives a false impression of security to those who actually have serious asymptomatic lesions.

Various methods of X-ray examination, including stereoscopic and plain celluloid films, paper films, fluoroscopy and microfluorography, have been used in tuberculosis case-finding. The improvement of fluoroscopic screen and proper dark room have greatly improved the accuracy of fluoroscopy. When the entire group must be examined and facilities for film-taking are not available as in China to-day, it is especially valuable because of its lower cost.

The prevalence of pulmonary tuberculosis among college students in various countries has been reported as one per cent or less. Survey in Peiping gives a prevalence of 6.3 per cent of males and 3.5 per cent of females among university students in 1942. The results of X-ray examinations reported differ widely not only because of actual variation in incidence depending upon the age and sex of the group and the size and location of the community, but also through failure in varying degree to demonstrate or recognize lesions actually present.

Although definitely useful under certain circumstances examinations taken with low-power machines do not give results comparable to those obtained with celluloid films and improved technique. Additional difficulty in the comparison of results arises from difference in interpretation due to variation in training and experience. However, it is perfectly safe to say that in China the incidence of pulmonary tuberculosis among students is definitely much higher than among students of countries in Europe and America, and the problem is much more serious.

It may be concluded that the universal application of X-ray examination to students of the adolescent group is an important measure in the campaign against tuberculosis, and an economically sound expenditure of public funds.

SUMMARY

A total of 17,155 students of various high schools and universities, between age 10 and 36, were examined fluoroscopically during the years 1944 to 1946; 13,327 were boys and 3,828 were girls. Of these, 996 boys and 188 girls were diagnosed to have active pulmonary tuberculosis. The prevalence of tuberculosis was 6.9 per cent for the total, 7.5 per cent for the boys and 4.9 per cent for the

girls. Below the age of 16 years, the prevalence was about the same for both sexes, but above that, both the total and specific morbidity rates of the boys were higher than those of the girls. Among these, 841 patients, or 71 per cent, had minimal lesions and about 27 per cent had moderate lesions. The percentage of patients with far advanced pulmonary lesions was only 2.1. More than 80 per cent of these cases were asymptomatic.

SUMARIO

La Tuberculosis Pulmonar en los Estudiantes Chinos

En 1944-1946 se examinó roentgenoscópicamente a un total de 17,155 estudiantes de 10 a 36 años de edad, de varias escuelas superiores y universidades: 13,327 varones y 3,828 mujeres. En 996 varones y 188 mujeres se diagnosticó tuberculosis pulmonar activa. La frecuencia de tuberculosis representó 6.9 por ciento para el total: 7.5 por ciento para los varones y 4.9 por ciento para las mujeres. Antes de los 16 años, la frecuencia fué aproximadamente idéntica para ambos sexos, pero de ahí para arriba, los coeficientes de morbilidad, tanto total como específica, fueron mayores en los varones que en las mujeres. Entre éstas, 841, o sea 71 por ciento, tenían lesiones mínimas, y aproximadamente 27 por ciento, moderadas. El porcentaje de enfermos con lesiones pulmonares muy avanzadas no pasó de 2.1. Más de 80 de estos casos eran asintomáticos.

Acknowledgment

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INHIBITION OF PRIMARY TUBERCULOSIS BY BCG¹

A Study in Children, Based on 13,470 Chest Roentgenograms

IRWIN S. NEIMAN AND ERHARD LOEWINSOHN

It is necessary, because of a certain confusion that exists in the literature concerning the term primary tuberculosis, that a clear definition be made for the purposes of this study. Primary tuberculosis consists of the response of the host to first exposure to tubercle bacilli (all references in this report are to pulmonary tuberculosis). When the invading organisms are in sufficient number, the body response is of a pathological nature which differs in degree in direct proportion to the number of bacilli gaining entrance and in inverse proportion to the general resistance of the host. The pathological response may vary from "no clinical manifestations" of the invasion to the so-called "progressive primary focus" which may have a fatal termination. Fortunately in most human beings, the primary process is clinically silent and more or less self-limiting. The only tangible evidence of its presence in a great majority of instances is a positive tuberculin reaction.

Recent reports (1) on BCG have emphasized the degree to which this vaccine prevents clinical tuberculosis. Clinically significant tuberculosis is usually of the secondary or reinfection type. Reinfection tuberculosis occurs, by definition, only in persons who have had a primary infection. The value of BCG as a preventive would be enhanced if it could be demonstrated that BCG inhibits primary tuberculosis. In the course of an experiment, some of the basic data of which have been previously published (2), some 13,000 chest X-ray films, the majority serial (table 1), have accumulated. It was thought that this material might show whether and to what degree BCG inhibits primary tuberculosis.

MATERIALS AND METHODS

The children in this study were either vaccinated with BCG four to six days after birth (total 1,417) or were not vaccinated and served as controls (total 1,414). The age and race distributions are given in table 2. All came from homes free of tuberculosis as proved by chest roentgenograms of all family members. However, it should be pointed out that all subjects lived in areas in Chicago that have high tuberculosis mortality rates (from 100 to 300 per 100,000 population). In other words, although their immediate environment was free of tuberculosis they lived in a tuberculous milieu. All children were observed at more or less regular semi-annual intervals from birth. At each visit the children were subjected to a physical examination, tuberculin test and chest roentgenogram.

Orthodox methods of interpretation of the chest roentgenograms were used.

¹ From the Tice Clinic of the Municipal Tuberculosis Sanitarium of Chicago and the Department of Pathology and Bacteriology, The Chicago Medical School, Chicago, Illinois.

The hilum was examined for density, enlargement and outline. Any evidences of abnormalities were noted and followed by frequent serial films to determine their nature. Parenchymal densities were noted and followed similarly. Only parenchymal densities which persisted for a period of months were included in the tabulations. Calcification was diagnosed only by characteristic formation, outline and refractility. (Examples of typical films are shown in figures 1 to 6.) In addition, the X-ray findings were correlated with the tuberculin reaction.

TABLE 1
Distribution of chest X-ray films

NUMBER OF X-RAY FILMS	VACCINATED WITH BCG	NOT VACCINATED
1	197	194
2	194	141
3	145	151
4	148	156
5	120	150
6	125	139
7	96	108
8	98	89
9	93	84
10	67	74
11	31	44
12	12	22
13	3	8
14	1	6
Total.....	6,443	7,027

RESULTS

The incidence of the various types of pulmonary tuberculosis in the two groups of children is shown under the column headed "Totals" in table 3. All findings in the non-vaccinated children were limited to those who reacted to tuberculin. Calcification, with no previous films showing definite involvement, occurred 3 times in the vaccinated and 5 times in the controls. In 4 of these 8 cases a film showing no definite findings is available within the immediately preceding six months and in the remaining 4 there were no available films for at least two years. In all but 3 instances of the 37 cases with evidence of pulmonary lesions other than calcification as a first finding, the tuberculin reaction became positive concurrently with the appearance of the abnormalities. In the 3 exceptions the tuberculin reaction was previously positive. The further data in table 3 are concerned with the end-result of the initial lesions. In the 11 cases among the vaccinated where initial lesions other than calcification were found, 8 have disappeared, one has calcified and 2 are now in a state of questionable calcification. None of the cases is now in an active state. On the other hand, of the

TABLE 2
Age and race distribution

OBSERVED FOR	RACE	VACCINATED WITH BCG	NOT VACCINATED
3 months*	Negro	945	978
	White	472	436
4 months	Negro	917	949
	White	466	431
8 months	Negro	901	942
	White	461	426
12 months	Negro	864	926
	White	454	422
1½ years	Negro	821	906
	White	450	418
2 years	Negro	784	880
	White	447	411
2½ years	Negro	740	846
	White	436	406
3 years	Negro	694	798
	White	418	390
3½ years	Negro	663	757
	White	402	379
4 years	Negro	602	689
	White	380	359
4½ years	Negro	554	627
	White	357	332
5 years	Negro	481	547
	White	330	306
5½ years	Negro	413	476
	White	287	280
6 years	Negro	356	393
	White	250	223
6½ years	Negro	286	310
	White	210	185
7 years	Negro	209	236
	White	150	128

TABLE 2—Continued

OBSERVED FOR	RACE	VACCINATED WITH BCG	NOT VACCINATED
7½ years	Negro	149	166
	White	98	79
8 years	Negro	98	117
	White	60	44
8½ years	Negro	61	65
	White	32	14
9 years	Negro	26	25
	White	10	5
Total	Negro	945	978
	White	472	436
Total		1,417	1,414

* Three months or less.

37 cases among the controls whose initial chest findings were other than calcification, 10 have disappeared, 9 have healed by definite calcification, 4 show questionable calcification and 12 are still in an active state.

Roentgenologically it is often not possible to label definitely a hilar change or a parenchymal density tuberculous unless certain other data are available. Not the least important is the tuberculin reaction. Because the tuberculin reactivity was available from birth in all cases under observation, and because of the absence of comparable chest findings in nonreactors among the controls, it is felt that in every instance the pulmonary lesion observed was on a tuberculous basis. However, since calcification is considered the most characteristic form of the healed primary lesion, the relative results in the two groups, vaccinated and controls, are considered worthy of further emphasis. Up to the present, 9 of the original 37 controls have calcified lesions, as compared to 1 out of the original 11 vaccinated children with X-ray findings. If we add to these the children who showed calcification with no previous roentgenological findings, the result is 14 among the controls and 4 among the vaccinated. In table 3 is also shown a category of questionable calcification. The 6 cases listed, 2 vaccinated and 4 controls, showed densities whose outline in a number of serial films over a period of months to years has remained constant, but whose refractility is not characteristic.

In table 4 is given a summary of the relative incidence of all findings in the two groups. It is to be noted that the incidence of all evidences of primary tuberculosis as defined here is considerably less frequent in the vaccinated group than in the non-vaccinated. Using the person-year device to equalize the two categories, the incidence ratio shows a total balance in favor of the vaccinated children. However, the number of cases in each category is so small as compared

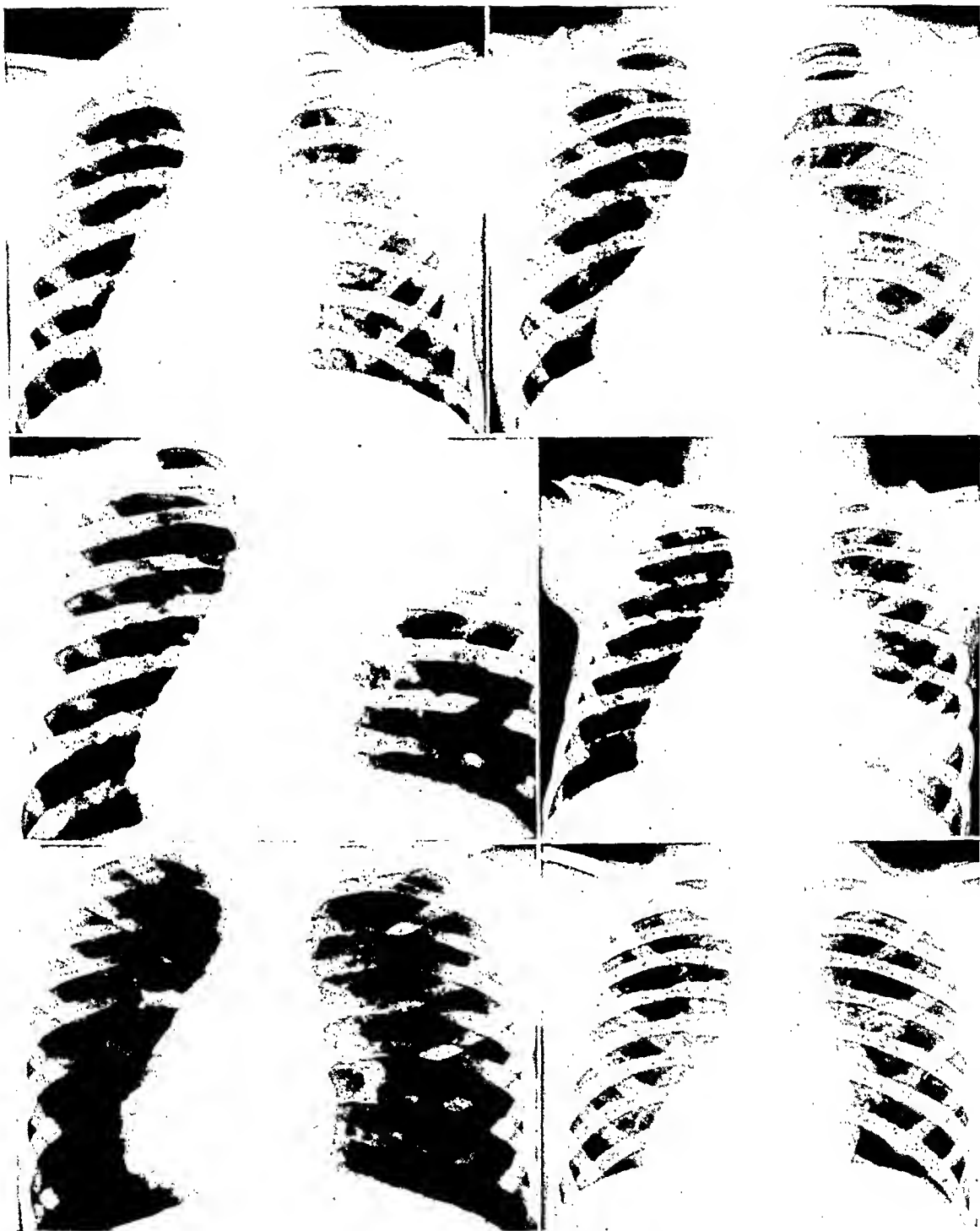


FIG. 1. (Upper left) Hilar involvement.

FIG. 2. (Upper right) Hilar involvement and visible right interlobar fissure.

FIG. 3. (Centre left) Parenchymal infiltrate.

FIG. 4. (Centre right) Parenchymal infiltrate.

FIG. 5. (Lower left) Hilar calcification.

FIG. 6. (Lower right) Parenchymal calcification.

to the total number of children that it was thought necessary to test the significance of the difference by a statistical formula. The commonly used Chi-square (X^2) test was applied. When a certain phenomenon, such as calcification, occurs in two groups who differ only by one character, then the value of X^2 will give the probability that the difference occurred by chance. The probability factor P may be read from tables provided in any text on medical biometry. In table 5 the X^2 value for each category and for the total number of cases of primary tuberculosis is indicated.

TABLE 3
Present status of initial lesions seen in chest roentgenograms

CHARACTER OF INITIAL LESION	GROUP	TOTAL	PRESENT STATUS				
			Disappeared	Calcification	Questionable Calcification	Still Active	Died
Hilar involvement	Vaccinated	8	5	1	2	0	0
	Control	23	6	5	3	9	0
Parenchymal densities	Vaccinated	3	3	0	0	0	0
	Control	13	4	3	1	3	2
Pleural effusion	Vaccinated	0	0	0	0	0	0
	Control	1	0	1	0	0	0
Calcification*	Vaccinated	3	0	3	0	0	0
	Control	5	0	5	0	0	0
Totals	Vaccinated	14	8	4	2	0	0
	Control	42	10	14	4	12	2

* These 8 children showed calcification with previous roentgenograms giving no indication of a lesion.

DISCUSSION

Results of observations on a controlled group of children vaccinated with BCG are presented. Brailey (3) and Rigler (4) have indicated that pulmonary X-ray changes of the same character as those defined in this study are of a tuberculous nature. High and Zwerling (5) have arrived at a similar conclusion. They also point out the relatively higher incidence of hilar adenopathy in the younger age groups. This conforms with the findings reported here as most of the cases are in the category with hilar involvement which is to be expected, since the oldest child in this study is 9 years of age and the average age for the group is 4.4. Kereszturi, Park and Logie (6) reported on the chest X-ray changes in BCG vaccinated and non-vaccinated children. These authors found that X-ray evidence of primary tuberculosis was present in a significantly higher incidence in non-vaccinated tuberculin-positive children than in those who received BCG. Rich (7) quotes this study as possible further evidence for the existence of acquired immunity in tuberculosis.

TABLE 4

Incidence of primary tuberculosis in BCG vaccinated and non-vaccinated children

	VACCINATED	NON-VACCINATED		RATIO OF INCIDENCE CONTROLS: VACCINATED PER 1,000 PERSON-YEARS
Total number of children.....	1,417	1,414		
Person-years observed.....	5,627	6,032		
		Reactors (356)	Non-reactors (1,058)	
Hilar involvement				
Number.....	8	23	0	2.68
Rate**.....	1.42	3.81	0	
Parenchymal densities				
Number.....	3	13	0	4.05
Rate.....	0.53	2.15	0	
Calcification				
Number.....	4	14	0	3.27
Rate.....	0.71	2.32	0	
Total number* of primary lesions				
Number.....	14	42***	0	2.83
Rate.....	2.46	6.92	0	

* Total is not a summation of three categories listed since calcification includes both those cases in which the deposition occurred following an initially visible lesion and as a first finding.

** Rate per 1,000 person-years.

*** Includes one case of effusion listed in table 3.

TABLE 5

X² tests of significance of differences

	X ²	P*	OPPORTUNITY FOR THIS FINDING TO BE DUE TO CHANCE
Hilar involvement.....	7.2115	0.0072	1:140
Parenchymal densities.....	6.2855	0.0122	1:80
Calcification.....	5.5908	0.0180	1:50
All types of primary tuberculosis.....	14.2825	0.0002	1:5000

* P = Probability that the difference could have occurred by chance.

The impression seems unavoidable that children vaccinated with BCG tend to show less primary tuberculosis as determined by roentgenographic examination. Utilizing only the data presented here, there is evidence that certain types of primary tuberculosis (increased and enlarged hilar density and paren-

chymal densities) are inhibited. All forms other than calcification depend upon a positive tuberculin reaction to confirm the diagnosis. Calcification in the pulmonary fields, unless proved otherwise, is most often considered to be on a tuberculous basis. If we confine ourselves, for the moment, to calcification alone as the criterion of primary tuberculosis, and refer again to table 4, it is noted that calcification occurred 3 times as frequently in controls as in vaccinated children. It may be argued that the number of cases is too small to be cited as conclusive evidence that this result is attributable to vaccination with BCG. And it must be pointed out that this argument is given a certain degree of support by the results of the Chi-square test (table 5). Statistically X^2 should be 4 or greater to indicate significance and should be 9 or greater to allay all doubts (8). In the case of calcification $X^2 = 5.5908$ which is only fairly good evidence of a difference of statistical significance. However, there are no cases among the vaccinated whose status is undetermined and there are 12 such among the controls. It is only reasonable to assume that some of these will show calcification with time and only serve to emphasize the ratio of incidence in favor of the vaccinated children. Furthermore, a recent report by Hardy (9), in which 230 children with roentgenological evidences of primary tuberculosis of the same character as the types described here, indicates that these findings are on a tuberculous basis. In view of this support, we may point out the fourth line of table 5 where the X^2 value for all types of primary tuberculosis seen roentgenologically is 14.2825 which is equivalent to a P value of 0.0002 and is statistically unquestionably significant of a real difference.

Myers (10) has admirably presented the case for eradication of tuberculosis by discovery and isolation of source cases. He has further shown that it is important to prevent primary infection because it is only in such persons that secondary tuberculosis develops. The point is quite correctly made that most often the only evidence of the presence of the primary disease is a positive tuberculin reaction. Under such circumstances the impression is gained that it is preferable to be a nonreactor to tuberculin, since this means no tuberculosis. This is unquestionably true and would be a practical method of tuberculosis control if it were possible to isolate every case of diagnosed tuberculosis. Unfortunately such a procedure is economically not feasible in many areas in the United States, and even more so in other countries. Furthermore, in highly urbanized and industrialized areas with high rates of low income groups and attendant poor hygienic conditions, it is not a goal that can be realized in the near future. Tuberculosis control programs having such an aim may be aided by the use of BCG vaccine as an adjunct to hasten the decline in the incidence of tuberculosis.

SUMMARY AND CONCLUSIONS

1. Up to the present time 13,470 chest roentgenograms have been taken on a group of 1,417 children vaccinated with BCG and a similar group of 1,414 children reserved as controls, all of whom were observed from birth.
2. Analysis of the films revealed a significantly higher incidence of primary tuberculosis, as evidenced by pulmonary abnormalities usually considered tuberculous, in the non-vaccinated children.

3. The results suggest that vaccination with BCG tends to reduce the incidence of primary tuberculosis and that BCG may be used as an adjunct to the already functioning tuberculosis control programs aimed at discovery and isolation of source cases.

SUMARIO Y CONCLUSIONES

Inhibición de la Tuberculosis Primaria con BCG

1. Hasta la fecha se han tomado 13,470 radiografías torácicas en un grupo de 1,417 niños vacunados con BCG, reservándose como testigos a un grupo semejante compuesto de 1,414 niños, y manteniéndose a todos en observación desde el nacimiento.

2. El análisis de las películas reveló una incidencia significativamente mayor de primo-tuberculosis, traducida por anomalías pulmonares habitualmente consideradas como tuberculosas, en los niños no vacunados.

3. El resultado indica que la vacunación con BCG tiende a rebajar la frecuencia de la tuberculosis pulmonar, y que puede utilizarse como adjunto de las obras de lucha antituberculosa ya en funcionamiento que buscan el descubrimiento y aislamiento de los casos primarios.

This study is in the nature of a progress report. A future report will be made to reevaluate the findings in the light of a longer period of observation and a greater number of cases.

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MORPHOLOGY OF THE MYCOBACTERIUM TUBERCULOSIS¹

A Study of Artifacts Produced in Smears

DIRAN YEGIAN AND JOSEPH KURUNG

The morphology of the tubercle bacillus presents a confusing picture. This is due in large part to the variants presented by the organism. Here one encounters a difference in terminology and conflicting opinions regarding their biological significance. However, for convenience, the variants may be divided into the following four groups: (a) the granular form, the most common modification of the solidly stained rod; (b) the beaded form; (c) Much's granules, distinguished from the previous groups by a special staining technique; and (d) the non-acid-fast fine rods and granules.

Recent studies (1, 2, 3, 4) indicate that only the granular form represents a biological variant of the tubercle bacillus and that the remaining three groups are in reality artifacts. The recognition of the artifacts is essential for a proper understanding of the morphology of the tubercle bacillus and for this reason will receive first consideration.

Beaded forms were the first morphological variant described and regarded as evidence of spore formation, resting cells or conidia (figure 1). The beads range in number from one to five in a single bacillus, are usually round and dark purple in color. They vary in size and may be large enough to distend the body of the bacillus. Under favorable focus the larger beads often exhibit less densely stained centres. Bead formation is dependent upon the composition and the concentration of the fuchsin dye used in the Ziehl-Neelsen staining procedure. Tubercle bacilli stained with the acetate dye show many beaded forms; with the hydrochloride they are absent or few in number. In weak concentrations of the hydrochloride dye (0.3 per cent) the bacilli are consistently solidly stained and beaded forms are not encountered. The addition of a small amount of sodium chloride to the staining solution produces a marked increase in the number of beaded forms. The beads are dissolved instantly by the application of 95 per cent ethyl alcohol or 5 per cent phenol. In a given bacillus they can be made to reform and disappear repeatedly and the reformed beads are often changed in size, number and location in the cell. Consideration of the factors underlying the formation of beads justifies the opinion recently confirmed by Lamanna (5) that they are artifacts. It will be shown later that they do not conform in behavior to stained morphological units of the organism.

Much's granules: The granules can be demonstrated by using a modified Gram staining technique. They were considered to be special non-acid-fast developmental forms of the organism. Later investigators have ascribed variable biological functions to these granules. They are deeply stained, spherical bodies which are irregularly distributed and as many as 12 may be seen in a single

¹ From the Ray Brook State Tuberculosis Hospital, Ray Brook, New York.

bacillus (figure 2). The granules differ from the beads in that they are not dispersed by the application of 95 per cent alcohol. They are, however, dispersed with 5 per cent phenol and the bacilli then become solidly stained. They can be dispersed and reformed in the same manner as the beads. It seems reasonable to assume that they belong to the same category as the beads.

Non-acid-fast forms: The presence of non-acid-fast rods and granules in young cultures of tubercle bacilli has been repeatedly observed and they are generally regarded either as stages in the reproductive cycle or as structural units of the bacillus. The non-acid-fast forms are readily demonstrated by the technique outlined by Kahn (6) and others which includes the use of a spatula or loop in spreading the preparation on the slide. It was found (4) that the application of the spatula or loop so traumatized the bacilli that they were rendered non-acid-fast (figure 3). In other words, one is here dealing with an artifact, the result of trauma.

Morphology of the tubercle bacillus: If the marginal portion of a thin 4- to 6-day-old membrane-like growth (figure 4) obtained by frequent transfer of tubercle bacilli, strain H37, on Long's synthetic medium, is stained as a whole mount by the Ziehl-Neelsen technique using the hydrochloride dye, the microorganisms appear solidly stained (figure 5). A slight difference in length and the degree of acid-fastness may be observed. However, if these young cells are treated with Loeffler's methylene blue on a wet cover slip preparation, deeply stained bodies, which may be nuclear bodies, can be demonstrated. They are usually two in number and are located at the polar ends (figure 6). These bodies are only occasionally visible with the Ziehl-Neelsen stain since the entire cell is intensely stained by this method. The short solidly stained rods are characteristic of tubercle bacilli undergoing normal reproduction by simple fission.

Pleomorphism occurs in older cultures as the result of unfavorable environmental conditions. The bacilli first become elongated but stain solidly (figure 7). Later the cytoplasm of the elongated cells separates into granules which occupy a fixed position in the cell (figures 8 and 9). The granular forms were first described by Marmorek (7) and later by Spengler (8) who named them *Splittern*. They were referred to as spores by Babes (9), Nocard and Roux (10), Metchnikoff (11) and Kronberger (12). Spengler later considered the spaces between the granules as possible spores but found that, upon culturing the *Splittern*, normal, solidly stained rods were obtained. These variants have been described by many other investigators but it is possible that in some instances they may have been dealing with the beaded form of the bacillus. The formation of the granules takes place gradually and their size and number varies with the length of the cell (figures 8 and 9). The granules stain strongly acid-fast and no stained material is visible between the granules unless the separation of the cytoplasm is incomplete. In this case a faintly stained line may be seen connecting two granules. Granular cells stained first by the Ziehl-Neelsen procedure and then outlined by nigrosine, a negative stain, show a white continuous border. This represents the cell wall which encloses the acid-fast granules. The separation of the cytoplasm into granules is brought about apparently by prolonged

unfavorable conditions in the culture medium and is a natural occurrence in the growth cycle. It seems likely that the change is due to a combination of conditions which exist in an old culture, such as deficient food and oxygen supply, crowding due to growth, and not to any single environmental factor.

Our studies indicate that a limited degree of metabolism must be maintained to accomplish the formation of granules. This can be illustrated by the following experiment. If a portion of thin membrane growth of tubercle bacilli is freed of medium and incubated on physiological salt solution, no growth occurs and the bacilli stain solidly. The addition of a small quantity of nutrient to the salt solution in the form of yeast extract, dextrose and glycerol, permits limited growth for seven to ten days. At this time the bacilli are found to be elongated and granular and resemble those observed in old cultures.

It seems likely that these cytoplasmic granules represent a means of protection for the cell but they cannot be considered analogous to classical spore formation, since there is evidence that the granular cells are no more resistant to heat than the young bacilli which stain solidly.

It is recognized that a great many morphological variants can be induced by intentional changes in the environment. The granular variation described is that observed during the normal growth cycle.

Until more is known concerning the factors causing this particular morphological change it would appear unwise to attach any clinical significance to the presence of granular bacilli in pathological material: Transfer of the granular cells to fresh medium results, after a period of incubation, in bacilli which stain uniformly acid-fast. It is possible to observe microscopically the gradual return of the granular cell to the solid form. The granules elongate and fuse into one homogeneous form and later the cell divides in the usual manner. Granules in all stages of fusion may be demonstrated in stained preparations (figure 10).

The granules described above differ from the beads in the following respects: (1) They are not dependent upon the concentration or composition of the dye used in staining. (2) They do not distend the cell and are irregular in shape. (3) They stain uniformly red while the interspaces are unstained. (4) They are not dispersed by treatment with alcohol or phenol.

FIG. 1. Beaded forms of tubercle bacilli.

FIG. 2. Much's granules.

FIG. 3. Portion of a 4-day-old growth membrane showing numerous non-acid-fast forms caused by the traumatic action of the platinum loop.

FIG. 4. Young growth membrane stained as a whole mount. Magnified $\times 30$.

FIG. 5. Cells from figure 4 stained with Ziehl-Neelsen technique.

FIG. 6. Cells from figure 4 stained with methylene blue showing polar bodies.

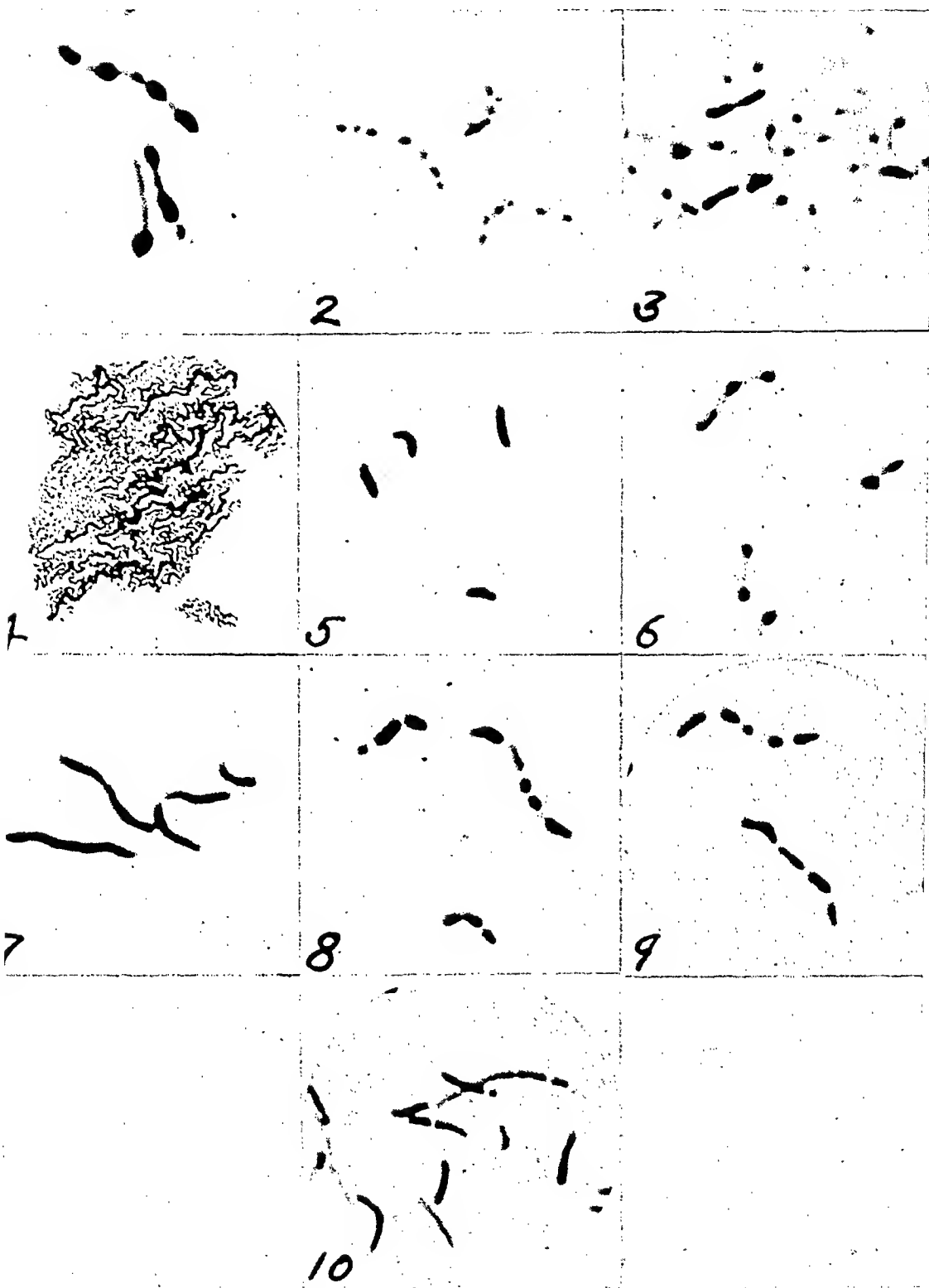
FIG. 7. Tubercle bacilli, 6 weeks old solidly stained and showing great variation in length as compared with the young cells in figure 5.

FIG. 8. Granular forms in 3-months-old culture.

FIG. 9. Granular forms in sputum.

FIG. 10. Cells from 3-month-old culture placed in Long's medium showing elongation of cytoplasm prior to division of cells.

All illustrations with the exception of figure 4 were taken at a magnification of 1200 and then enlarged three times.



FIGS. 1-10

SUMMARY

The elimination of artifacts by proper staining solutions and by the avoidance of trauma in the preparation of the film greatly simplifies the study of the morphology of the tubercle bacillus. Rapidly growing tubercle bacilli are solidly stained by the Ziehl-Neelsen technique, attention being given to the composition and concentration of the dye. In older cultures the conditions for growth are unfavorable and the bacilli first become elongated and then granular. The granules represent morphological units of the bacillus and are readily differentiated from the artifacts.

SUMARIO

Morfología del Mycobacterium tuberculosis

La eliminación de artefactos por medio de soluciones apropiadas de coloración y de la supresión de traumatismos en la preparación de la película simplifica considerablemente el estudio morfológico del bacilo tuberculoso. Los bacilos en vías de rápido desarrollo quedan sólidamente teñidos con la técnica de Ziehl-Neelsen, si se presta atención a la composición y concentración del colorante. En los cultivos más viejos no son favorables las condiciones para el desarrollo y los bacilos, después de alargarse, se vuelven granulares. Los gránulos representan unidades morfológicas del bacilo, y se diferencian sin dificultad, de los artefactos.

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STREPTOTHRICIN IN EXPERIMENTAL TUBERCULOSIS¹

Its *in vivo* Activity and Toxicity for Guinea Pigs and Hamsters Infected with *Mycobacterium tuberculosis*

W. STEENKEN, JR. AND PHILIP F. WAGLEY

Streptothricin,² an antibiotic with many properties in common with streptomycin, has been reported as both mycobacteriostatic and mycobacteriolytic (1, 2). Several workers (3, 4) have found it relatively nontoxic for both mice and guinea pigs. Consequently, it seemed advisable to use streptothricin for the treatment of tuberculous infection in certain experimental animals.

MATERIALS AND METHODS

Each of 40 tuberculin-negative guinea pigs weighing about 500 g. was inoculated with approximately 30,000 tubercle bacilli, strain H37 Rv. The tubercle bacilli were obtained from 14-day-old cultures grown on Proskauer and Beck's synthetic fluid medium. The infected guinea pigs were divided into four groups (A, B, C, D) of 10 animals each. Those in group A received no treatment and served as nontreated controls. Each animal in group B received 1,000 units³ of streptothricin intramuscularly on the day of infection, and 500 units daily thereafter in the same manner for seventeen days. The dose was then increased to 1,000 units per day. The animals in group C received 1,000 units of the drug intramuscularly on the day of infection, and 500 units in the same manner on alternate subsequent days. After administration of a total of 4,000 units, the dose was increased to 1,000 units per day. The animals in group D received no treatment until seventeen days following inoculation. They were then given intramuscularly 1,000 units daily. Seventy-one days after the infecting dose all treatment was discontinued because of toxic manifestations of the drug. This interruption of drug therapy lasted for twenty-five days, when therapy was again started and continued for an additional fifty-seven days. All surviving animals were skin tested with 5 per cent OT and then killed. The duration of the experiment was 153 days.

Each of 20 golden hamsters (*Cricetus auratus*) weighing about 100 g. was inoculated subcutaneously in the left inguinal region with 60,000 tubercle bacilli, strain H37 Rv, obtained from a 14-day-old culture grown on Proskauer and Beck's synthetic fluid medium. Each of 30 hamsters was inoculated similarly with 30,000 tubercle bacilli, strain H37 Rv. One-half of each group was started immediately on intramuscular daily doses of 250 units of streptothricin. After four days, treatment was discontinued because of signs of toxemia. Three days later treatment was resumed with daily doses of 125 units per animal. After forty-seven days of therapy all treatment was omitted for twenty-five days and then resumed according to schedule (125 units per day per animal intramuscularly), and continued for an additional fifty days. Occasionally, in those animals showing the most severe toxemic signs, treatment was omitted until improvement occurred.

¹ From the Research and Clinical Laboratory, Trudeau Sanatorium, Trudeau, New York.

² The drug was supplied as streptothricin hydrochloride through the courtesy of Dr. J. Carlisle of Merck and Company, Rahway, New Jersey.

³ A unit of streptothricin has been defined (3) as the "minimum quantity of drug which, when added to 10 cc. of nutrient broth, will inhibit a given strain of *E. coli*."

On the twenty-fourth day of infection all hamsters were skin tested by the intracutaneous injection of 5 mg. of OT. As reported previously (5), a skin reaction could not be demonstrated. On the 126th day of infection all surviving hamsters were killed.

The following rating of the degree of tuberculous involvement was applied to both the guinea pigs and the hamsters. At autopsy the tuberculous involvement of the spleen, liver, lungs and lymph nodes was expressed in values proportionate to the extent and severity of the disease. The maximum rating of 4 in any organ was used to indicate wide-spread caseous disease. The maximum rating of 16 for the animal as a whole signified advanced generalized tuberculous.

TABLE 1
Guinea pig experiment

GROUPS OF ANIMALS	DEGREE OF TUBERCULOSIS				TOTAL DEGREE OF TUBERCULOSIS
	Lungs	Liver	Spleen	Glands	
A Untreated controls	2.0	2.5	3.7	3.4	11.6
D Delayed treatment	1.0	1.6	3.1	2.8	8.5
B Immediate treatment	2.3	3.3	3.8	3.5	12.9
C Immediate treatment and every other day	2.5	2.3	3.5	2.9	11.2

ANTITUBERCULOUS ACTIVITY OF STREPTOTHRICIN IN GUINEA PIGS

At the end of the experiment all control animals were alive. Of the 10 animals in group B given treatment immediately and every day thereafter, only 4 survived for 153 days. The remainder died between the seventy-seventh and the 146th day of infection, each animal having received a total of 62,500 to 105,500 units of streptothricin. Of those animals in group C, 7 survived the experimental period. The earliest death occurred 128 days after inoculation (each animal having received a total of 44,000 units). Only 3 animals of group D survived the experimental period. The remainder died from fifty-three to 102 days after treatment was begun, each animal having received various total dosages of 53,000 to 77,000 units, depending upon the ability of the animal to tolerate the drug.

Despite the high incidence of early deaths among the treated animals, the tuberculous infection in those groups was almost as extensive as that found in the longer lived animals of the control group (see table 1).

Intrautaneous injection of 5 mg. of OT on the forty-fourth day of infection into the animals of groups A and B caused extensive redness, edema and necrosis in all.

TOXICITY OF STREPTOTHRICIN FOR GUINEA PIGS

Although at the time of death there was marked evidence of tuberculous infection in the treated animals, certain observations suggested that the drug itself might have been at least a contributory fatal factor.

There was a rapid and marked loss of weight in the treated animals. Anorexia was noticeable and weakness striking. There was gross hematuria during both early and late phases of treatment. The hemoglobin level in the controls did not fall but was on the average of 15 to 20 per cent lower in the treated animals after receiving approximately 40,000 units of the drug. Another group of animals not reported here but receiving intramuscular injections of 850 units every eight hours developed bloody diarrhea after only three days of treatment.

Autopsy revealed not only the evidence of tuberculosis as indicated numerically in table 1 but other lesions for which the infection could not be held accountable. Scattered through the submucosa of the bladder were petechiae. Small, punctuate, non-indurated ulcerated areas were occasionally present in the mucosa of both the intestines and bladder. Such lesions were not observed in the controls.

TABLE 2
Hamster experiment

GROUPS OF ANIMALS	DOSAGE OF MICRO-ORGANISMS	DEGREE OF TUBERCULOSIS				TOTAL DEGREE OF TUBERCULOSIS
		Lungs	Liver	Spleen	Glands	
Controls.....	30,000	.67	1.04	.89	1.45	4.05
Treated.....	30,000	.73	.7	1.0	1.5	3.93
Controls.....	60,000	.85	.92	1.14	1.92	4.83
Treated.....	60,000	.75	.87	.8	1.2	3.62

ANTITUBERCULOUS ACTIVITY OF STREPTOTHRICIN IN HAMSTERS

As has been pointed out previously (5), the resistance of the hamster to large inocula of virulent tubercle bacilli is striking. As this work was being done before such information was available, larger inocula of tubercle bacilli were not used. The degree of tuberculosis in the treated hamsters was indistinguishable from that of the control animals as shown in table 2.

Intracutaneous injection of 5 mg. of OT on the twenty-fourth day of infection into all the hamsters caused no edema or necrosis in any of the animals (5).

TOXICITY OF STREPTOTHRICIN FOR HAMSTERS

Anorexia, weight loss and weakness were marked among the treated animals. Gross hematuria was observed early in treatment among those animals that died. Ten of the 30 treated animals died before termination of the experiment as contrasted with 4 deaths among the controls. No parenchymal lesions other than those explained by tuberculosis were found in the liver, heart, kidney, spleen,

lung, lymph nodes or intestines of the treated animals. Occasionally, the bladder of the treated animals during the experiment showed lesions similar to but not so extensive as those found in the guinea pigs. The treated animals alive at the end of the experiment showed no lesions other than those associated with the tuberculous infection.

DISCUSSION

Since this work was completed Feldman and Hinshaw (6) have reported the results of treating 6 tuberculous guinea pigs subcutaneously with 3,500 units of streptothricin daily in four divided doses immediately after inoculation with 0.1 mg. of tubercle bacilli. Treatment was temporarily discontinued after the fifteenth injection (a total of 13,125 units having been given) because of toxemic signs, some of which were similar to those reported here. A reduced dose of streptothricin (1,750 units a day) was tolerated poorly by their animals. Edema of the external genitalia, prolapse of the rectum and liver damage were observed by these workers in their animals. The degree of tuberculosis did not appear to be modified by treatment with streptothricin.

The degree of toxemia reported here was more severe than that observed by Metzger *et al.* (4) in guinea pigs with brucellosis and treated with streptothricin. Their animals were treated intraperitoneally and subcutaneously with 100 mg. of streptothricin every five days for four weeks until a total dosage of 600 mg. had been administered. There is no comment in their paper of toxemic manifestations. Robinson *et al.* (3) have given as much as 30,000 units per kg. of body weight to mice orally, subcutaneously, and intravenously in single doses and observed no toxemic effects over a period of five days. The preparations used were crude, varying from 5,000 units to 300,000 units per gram of material. Emmart (7) has reported streptothricin as more toxic than streptomycin for chick embryos.

Although streptothricin has been found efficacious in the treatment of some experimental bacterial infections (3, 4) in amounts not exceeding and sometimes far less than the toxic dose, it does not appear to be of value in the treatment of experimental tuberculosis.

SUMMARY

Streptothricin in doses large enough to be toxic for guinea pigs and hamsters has, in the schedules outlined, been ineffective in the treatment of experimental tuberculosis. These results are in contrast to the possible efficacy of this bactericidal and fungicidal substance in the treatment of other experimental infections.

SUMARIO

La Estreptomicina en la Tuberculosis Experimental

La estreptomicina, a dosis suficientemente grandes para resultar tóxicas para los cobayos y los hamsters, fué, con la posología descrita, ineficaz en el tratamiento de la tuberculosis experimental. Este resultado se halla en contraposición

con la posible eficacia de dicha sustancia bactericida y fungicida en el tratamiento de otras infecciones experimentales.

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EFFECT OF STREPTOTHRICIN ON MYCOBACTERIA¹

A Study of Its *in vitro* Activity and a Comparison with the Activity of Tyrothricin, 4,4'-diaminodiphenylsulfone, Diasone and Promin

PHILIP F. WAGLEY AND W. STEENKEN, JR.

A variety of molds have been reported (1, 2, 3, 4, 5) that produce antibiotic substances effective to various degrees in inhibiting multiplication of the tubercle bacillus.

One of these antibacterial drugs is streptothricin, an antibiotic substance obtained from actinomycetes (6). It is a nitrogenous, rather thermostable compound, not affected by proteolytic enzymes, and quite effective against a variety of gram-negative organisms (6). Although some workers (7, 8, 9) have found it toxic for guinea pigs, hamsters and chick embryos, others (10, 11) have reported it as relatively nontoxic for guinea pigs and mice. *In vitro* studies have shown that it may have mycobacteriostatic and mycobacteriolytic activity.

This is a study of the *in vitro* effect of streptothricin on certain strains of mycobacteria. Observations of factors that might influence its activity such as media, initial hydrogen ion concentration and strain of microorganisms are reported. The activity of streptothricin is compared with that of certain other antibacterial substances.

MATERIALS AND METHODS

Four different acid-fast microorganisms were studied: the human strains of *Mycobacterium tuberculosis*, H37 Rv and H37 Ra; the avian strain of *Mycobacterium tuberculosis*, A30; and the saprophyte, *Mycobacterium phlei*. The media employed were Proskauer and Beck's synthetic medium, Steenken and Smith's solid medium and Dubos' fluid medium (13). The media were adjusted to pH 6.2 or 7.2. The streptothricin contained between 150 and 300 units² per milligram. The antibacterial drugs³ employed were incorporated directly in the media. Growth has been recorded in one of two ways: (1) in terms of square millimeters or surface growth or (2) in percentage of transmission of light by cultures in Dubos' medium as measured with a Klett-Summerson colorimeter (15). All original transplants were made from 14-day-old cultures growing on Proskauer and Beck's synthetic fluid medium. All tests were run in duplicate.

RESULTS

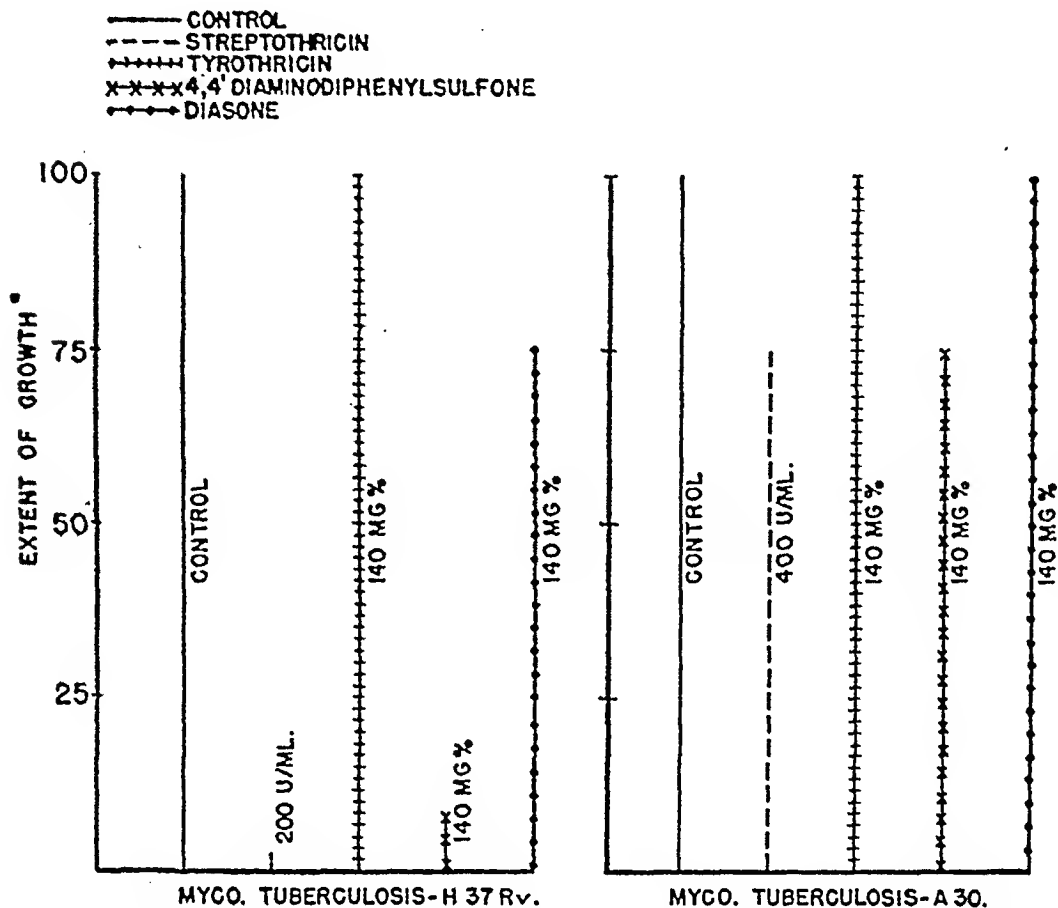
The growth pattern of *Mycobacterium phlei* was studied on Proskauer and Beck's synthetic fluid medium at pH 7.2 and pH 6.2 both in the absence and in the presence of various concentrations of streptothricin. The growth was

¹ From the Research and Clinical Laboratory, Trudeau Sanatorium, Trudeau, New York.

² A unit of streptothricin has been defined as the minimum quantity of drug which, when added to 1.0 cc. of nutrient broth, will inhibit a given strain of *E. coli* (11).

³ Tyrothricin and streptothricin were received through the courtesy of Dr. J. Carlisle of Merck and Company, Rahway, New Jersey. Promin, diasone and 4,4'-diaminodiphenylsulfone were furnished through the courtesy of Parke, Davis and Company, Detroit, Michigan.

measured every other day and recorded in square millimeters. Streptothricin in concentrations of 1 to 100 units per ml. at pH 7.2 caused no appreciable decrease in the rate of growth. However, at pH 6.2 successively increasing concentrations of streptothricin (1, 10 and 100 units per ml.) caused exaggeration of the initial lag in rate of growth. The control at pH 6.2, after an initial



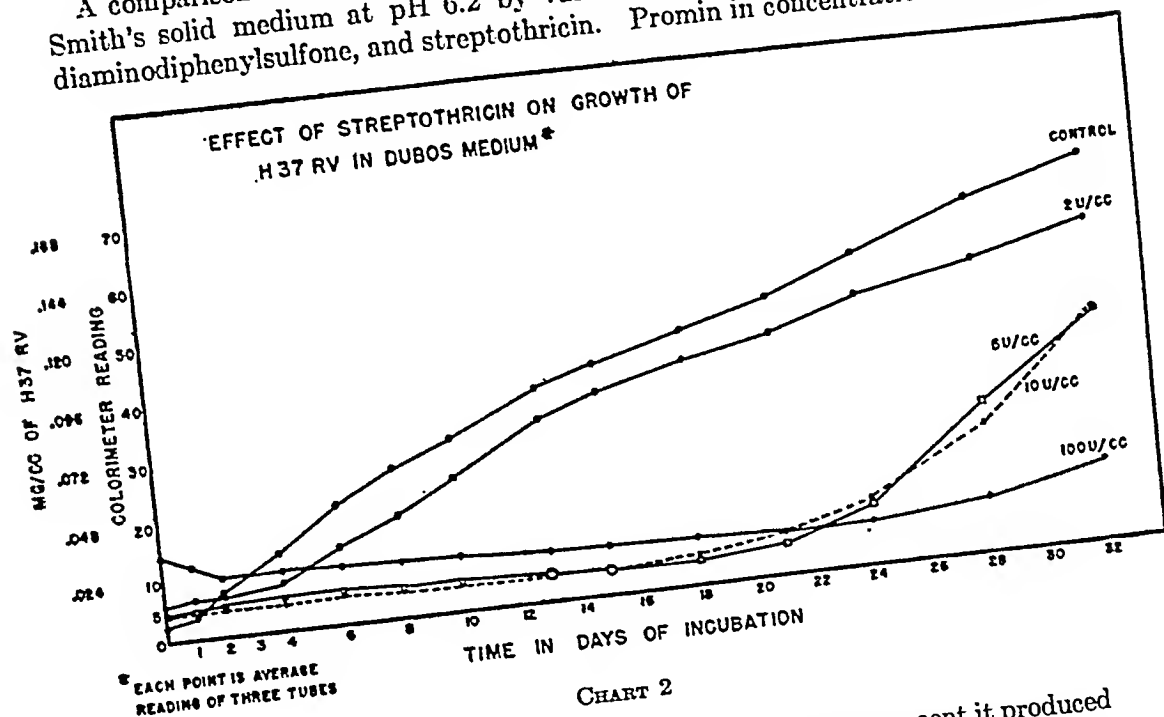
* AS DETERMINED BY SIZE OF GROWTH AT END OF TEN WEEK PERIOD AND EXPRESSED IN PERCENTAGE OF GROWTH SIZE OF THE CONTROLS.

CHART 1

lag period of seven days, showed extensive growth (about 10,000 square mm.) on the fourteenth day. In the presence of 100 units of streptothricin per ml. there was no appreciable growth even at the end of twenty-five days; then over a period of twenty days the rate of growth of such cultures became quite rapid and attained the size of those of the controls. Those cultures containing lower concentrations of streptothricin at pH 6.2 showed similar growth patterns but deviated less from the controls in rate of growth. The growth patterns of H37 Rv and H37 Ra on Proskauer and Beck's synthetic fluid medium at pH 7.2 and pH 6.2 in the absence and in the presence of various concentrations (1, 10 and 100 units

per ml.) of streptothricin were studied. (The cultures were read every two days and recorded in square millimeters.) In concentrations as high as 100 units per ml., streptothricin had little or no effect upon the rate of growth at pH 7.2. Only in concentrations of 100 units per ml. and at pH 6.2 did streptothricin exert marked inhibition of the initial rate of growth for the first twenty-four days. During the succeeding twenty-day period, however, the growth became quite rapid and attained the size of the controls.

A comparison was made of the effects on growth of H37 Rv on Steenken and Smith's solid medium at pH 6.2 by various concentrations of promin, 4,4'-diaminodiphenylsulfone, and streptothricin. Promin in concentrations of 2 and



5 mg. per cent produced no inhibition of growth. At 40 mg. per cent it produced only 50 per cent diminution in growth. Diaminodiphenylsulfone in concentrations of 2, 5 and 40 mg. per cent produced a 50, 75 and 90 per cent diminution of growth, respectively. Streptothricin in concentrations of 5 units per ml. caused 90 per cent less growth. Ten units per ml. almost completely inhibited growth and no growth occurred with 100 units per ml. Readings were made on the average of every four days. The final readings were made at the end of forty-four days. The growth of H37 Ra when studied in the above circumstances was modified in an almost identical manner.

The growth pattern of *Mycobacterium phlei* was recorded over a period of forty-four days on Steenken and Smith's solid medium at pH 6.2 in the absence and in the presence of various concentrations of streptothricin. Five units per ml. caused a prolonged lag in growth. Ten units per ml. caused almost complete inhibition and no growth occurred with 100 units per ml. of medium. This

degree of inhibition of *Mycobacterium phlei* was much greater than that seen for the same organism on Proskauer and Beck's medium at pH 6.2.

Chart 1 presents the effects of streptothricin, tyrothricin, 4,4'-diaminodiphenylsulfone and diasone on the growth of the human strain H37Rv and the avian strain A30. The cultures were grown on Steenken and Smith's solid medium at pH 6.2. Readings were made on the average of once a week for ten weeks. Streptothricin and 4,4'-diaminodiphenylsulfone in very high concentrations exerted a marked inhibition of the growth of H37Rv but very little effect on the growth of the avian strain A30. High concentrations of tyrothricin and diasone had no significant effect on the growth of either strain.

Chart 2 presents the effect of various concentrations of streptothricin on the submerged growth of H37Rv in Dubos' liquid medium at pH 7.2.

DISCUSSION

The concentration of streptothricin necessary to inhibit the growth of these particular strains of mycobacteria was relatively high when compared with those concentrations necessary to prevent growth of the strains studied by Woodruff and Foster (12). They observed that one unit of streptothricin per milliliter of Long's medium markedly diminished the growth of several strains of mycobacteria. This difference in effective bacteriostatic titer may be due to differences in the media employed or in the strains studied.

A high pH has been found to enhance the antibacterial activity of streptothricin for *E. coli* (14). From this observation the conclusion was made that the streptothricin molecule was most effective in the undissociated state. It is of interest that the experiments reported here suggested that streptothricin was slightly more inhibitory during the early growth period for *Mycobacterium tuberculosis* H37Rv and H37Ra and *Mycobacterium phlei* at 6.2 than at a pH 7.2 in Proskauer and Beck's synthetic fluid medium.

That media may have a definite influence on the antibacterial action of streptothricin was suggested by the enhanced effectiveness of the drug against H37Rv, H37Ra and *Mycobacterium phlei* when they were grown on Steenken and Smith's solid medium (pH 6.2). Concentrations as low as 5 units per ml. markedly inhibited growth. This effectiveness is in contrast to the relatively poor antibacterial effect of the drug in Proskauer and Beck's medium at both pH 7.2 and pH 6.2.

Serial and frequent studies during the course of growth demonstrated that effective concentrations in Proskauer and Beck's medium were only inhibitory during the initial stages. Following a prolonged period of growth lag the colonies multiplied rapidly to attain sizes comparable to those of the controls. Such patterns were followed by the growth of H37Rv, H37Ra and *Mycobacterium phlei*. On Steenken and Smith's solid medium *Mycobacterium phlei* in the presence of 5 units per ml. demonstrated a similar pattern. With higher concentrations of streptothricin in the latter medium no such terminal increase in rate of growth of any of the strains was evident during the periods of observation.

Streptothricin inhibited the growth of H37Rv more than did diasone, tyrothri-

cin, 4,4'-diaminodiphenylsulfone, or promin under the circumstances of the experiment. However, very large concentrations of the first four drugs exerted no striking effect on the growth of the avian strain of *Mycobacterium tuberculosis*, A30, suggesting that there may be a type difference in resistance to streptothricin.

SUMMARY

1. Streptothricin, under specified *in vitro* circumstances, inhibited the growth of H37Rv, H37Ra and *Mycobacterium phlei*.

2. This inhibitory effect was modified by pH, media, time and type of mycobacteria.

3. In the concentrations employed, streptothricin was more bacteriostatic than tyrothricin, 4,4'-diaminodiphenylsulfone, promin and diasone.

4. There were differences in the degree of resistance to streptothricin between the avian strain, A30, the saprophyte, *Mycobacterium phlei*, and the human strains, H37Rv and H37Ra.

SUMARIO

Efecto de la Estreptomina sobre las Micobacterias

1. La estreptomina, en ciertas circunstancias estipuladas *in vitro*, inhibió el desarrollo de H37Rv, H37Ra y *Mycobacterium phlei*.

2. Este efecto inhibitorio fué modificado por el pH, los medios, el tiempo y el tipo de las micobacterias.

3. A las concentraciones empleadas la estreptomina resultó más bacteriostática que la tirotricina, la 4,4'-diaminodifenilsulfona, la promina y la diasona.

4. Hubo diferencias en el índice de resistencia a la estreptomina entre la cepa aviaria, A30, el saprófito, *Mycobacterium phlei*, y las cepas humanas, H37Rv y H37Ra.

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EFFECT OF THYROID ON EXPERIMENTAL TUBERCULOSIS

R. A. IZZO¹ AND V. H. CICARDO¹

Many investigators admit that the thyroid gland plays an important part in the development of tuberculosis. In general terms, it is admitted that this gland increases the resistance to tuberculosis and that improvement of exophthalmic goiter aggravates preëxisting tuberculosis. Notwithstanding the clinical and experimental evidence which confirms these impressions, some authors still doubt whether hyperthyroidism exerts a beneficial effect on the development of tuberculosis; they maintain that this action is not clear and that experimental investigations have not provided definite proof for this opinion.

In 1853 Hamburger stated that people with endemic goiter never fell ill with tuberculosis, while those who cured their struma often did. He claimed further that in phthisical patients who developed goiter, the tuberculous lesions tended to fibrosis and not to caseation. The inaccurate knowledge of glandular hypo- or hyperfunction explains the curious therapeutic deductions arrived at during that period, which consisted in the belief that patients suffering from tuberculosis should be sent to a goitrous region in order to provoke a struma.

PATHOLOGICAL STUDIES

The development of pathological anatomy has proved the accuracy of the conclusions arrived at by Virchow and Rokitansky during the past century. According to these authors, tuberculosis of the thyroid gland is rare and tuberculous lesions in the thyroid gland are generally due to invasion from infected surrounding tissues.

In 1900, Torri injected bacilli of the human type directly into the thyroid artery of dogs; the animals succumbed fifteen to twenty-nine days later; necropsy findings revealed the picture of generalized miliary tuberculosis. Microscopically the thyroid gland showed abundant hyperproduction of colloid substance together with an active epithelial proliferation, and in some cases new formation of follicles, not only in the injected lobe, but also in the opposite one. In the injected portion, caseous nodules with interstitial thyroiditis were found in smaller numbers than in any of the other organs. While the bacilli were very scarce in the colloid substance, they abounded in the vessels and surrounding tissues; they were short, granular and clearly showed degenerative changes; these bacilli were difficult to stain. The conclusions arrived at by this author were that the colloid substance possesses strong bactericidal properties, and that the thyroid gland reacts to the infection with a hypersecretion of colloid material, thus defending the organism from the sequelae of infection.

In experimental tuberculosis of guinea pigs, Gloyne (1925) found that the thyroid gland was infected in only one out of over 260 autopsies. This author also proved that the thyroid substance has no bactericidal action *in vitro*, and

¹ Centro de Investigaciones Fisiológicas, Hospital Tornú, Buenos Aires, Argentina.

that its injection into guinea pigs and rabbits with experimental tuberculosis did not stop the disease in the course of a few weeks. From these results he concluded that a direct action of the thyroid gland on tuberculous infection was highly improbable, and that the absence of lesions must be attributed rather to anatomical conditions, which allow it to escape infection. Gloyne pointed out that, on account of their relative immunity to tuberculosis, the behavior of heart and striated muscles may be compared with that of the thyroid gland.

Pathological studies of the thyroid gland have led Rona (1925) to the conclusion that the nodules which are sometimes found in this gland in miliary tuberculosis do not tend to progress, but, on the contrary, soon become encapsulated before reaching macroscopic size. Caseous tuberculosis is said to be extremely rare.

Coller and Huggins (1926) reported tuberculosis only 5 times in 1,200 goiters; Smith and Leech (1928) reported 3 cases with microscopic evidence of tuberculosis in 1,500 goiters removed surgically from patients who did not show any other tuberculous lesions. However, Seed (1935) did not find any tuberculous lesions in 1,400 goiters. That tuberculosis of the thyroid gland is rare has also been pointed out by Louria and Louria (1938), Vivoli and associates (1937), Lissner (1934), etc. From his experimental studies *in vitro*, Lissner draws the conclusion that the thyroid gland has no bactericidal effect on tubercle bacilli.

EXPERIMENTAL STUDIES

Frugoni and Grixoni (1909) infected rabbits with human type tubercle bacilli and gave them thyroidin tablets in a dosage that increased the metabolic rate. They found that, when large quantities of bacilli were injected, the test rabbits died as a result of toxemic phenomena before specific anatomical lesions had developed, while the rabbits which had been given thyroidin lived long enough to reveal the presence of tuberculous nodules. These authors also found that, if the dosage of bacilli was large enough to provoke chronic tuberculosis, the animals treated with thyroidin not only lived longer than the others, but some did not die of the infection.

Removal of the thyroid gland seems to aggravate experimental tuberculosis of the guinea pig. Webb, Gilbert and Ryder (1922) noted that thyroidectomized animals inoculated with tubercle bacilli died sooner and presented more intense lesions than the control animals. Similar results were obtained by Kallós and Kentzler (1932) and by Viethen (1936). Opposite views were advanced by Ferrata (1923), who found that thyroidectomized guinea pigs lived one week longer than the control animals. Schedtler (1934) inoculated thyroidectomized guinea pigs and observed a more benign course of tuberculosis than in normal animals. Salvioli (1924) reported conflicting results in partially thyroidectomized dogs.

According to Ocariz (1935), the injection of thyroid hormones into tuberculous guinea pigs accelerated their death, due to the increase of their metabolic rate.

From the foregoing one may draw the conclusion that, in general, investigators consider patients with hyperthyroidism to possess a greater resistance to tuber-

culosis, and cases with thyroid deficiency to be more susceptible to it. However, the discordant results of some authors require further investigation in order to obtain confirmatory evidence of certain as yet controversial points, and to ascertain definitely whether thyroxin treatment does or does not increase the animal's resistance to tuberculosis. It was, therefore, decided to investigate again the resistance to tuberculosis of both thyroidectomized guinea pigs and of animals with experimental hyperthyroidism caused by thyroxin injections.

METHODS

The survival time was determined of: (1) 20 thyroidectomized guinea pigs; (2) 20 guinea pigs with hyperthyroidism; and (3) 20 control animals, after each had been injected with 1 mg. of moist tubercle bacilli of the human type.

Total thyroidectomy had been done two weeks before inoculation. Infection was produced when the animals had completely recovered from the operation. In order to prevent the development of parathyroid insufficiency, the thyroidectomized guinea pigs received a diet consisting of plenty of milk, to which a solution of calcium salts had been added and, in addition, one unit of parathyroid hormone was injected intraperitoneally three times a week.

Hyperthyroidism was provoked by the injection of 30 micrograms of thyroxin twice a week. In 10 of the 20 animals with experimental hyperthyroidism, this treatment was initiated twenty days before inoculation, while in the remaining 10 animals thyroxin was started simultaneously with inoculation of the bacilli.

Postmortem examination was done immediately after death; the type and extent of the lesions, as well as the histological changes, were recorded.

RESULTS

The susceptibility to tuberculous infection of thyroidectomized guinea pigs became evident within the first month after the inoculation of the bacilli, during which 7 died, while only one death occurred among the control animals; none of those treated with thyroxin died; that is, of the thyroidectomized guinea pigs, 30 per cent died and of the controls only 5 per cent. During the third month, the difference still continued to be evident; 75 per cent of thyroidectomized animals died, 60 per cent of the controls and only 15 per cent of the animals with hyperthyroidism. During the seventh month, all of the thyroidectomized and control animals had succumbed, but there were 15 per cent survivors among those treated with thyroxin (see table 1 and chart 1).

Among the animals treated with thyroxin, those that had been injected twenty days before the inoculation of tubercle bacilli revealed a greater resistance to the infection during the first months than did those that had received thyroxin and bacilli simultaneously. Thus, the 2 deaths which occurred during the second month belonged to the latter group, out of which 8 animals died during the fifth month, as well as 4 others which had received thyroxin treatment a few days before infection. However, the 2 survivors which died during the

ninth month belonged to the group which had been simultaneously inoculated (see table 2)

TABLE 1

Deaths of thyroidectomized guinea pigs injected with thyroxin, and of controls inoculated with tubercle bacilli at the same time

MONTH	THYROIDECTOMIZED		INJECTED WITH THYROXIN		CONTROLS	
	Died	Per cent dead	Died	Per cent dead	Died	Per cent dead
1st	7	30	—	—	1	5
2nd	12	60	2	10	9	40
3rd	15	75	3	15	12	60
4th	16	80	9	45	17	85
5th	17	85	12	60	18	90
6th	17	85	13	65	18	90
7th	20	100	17	85	20	100

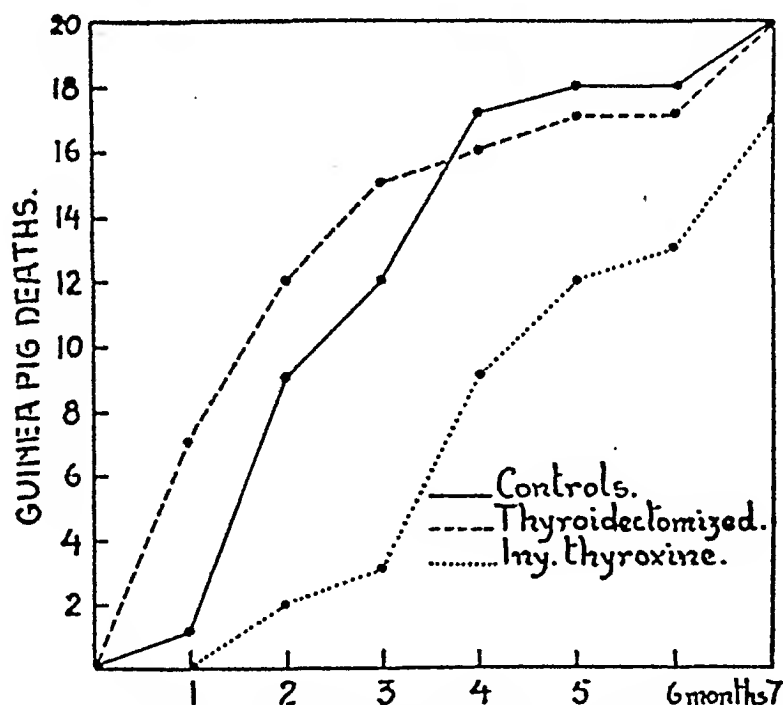


CHART 1. Deaths of thyroidectomized tuberculous guinea pigs injected with thyroxin, and of controls.

The pathological findings also revealed greater intensity and larger extent of the lesions in the thyroidectomized animals than in the controls which had died during the same period. In the animals which had died during the first months

as a result of toxemia, the anatomical findings did not reveal any extensive specific lesions.

The animals with artificial hyperthyroidism provoked by thyroxin administration, which outlived the controls, showed tuberculous nodules, the extent of which was generally related to the time of their survival.

TABLE 2

Deaths of tuberculous guinea pigs

Group 1 treated with thyroxin twenty days previous to inoculation of tubercle bacilli
Group 2 injected simultaneously with thyroxin and tubercle bacilli

MONTH	GROUP 1 ANIMALS TREATED WITH THYROXIN TWENTY DAYS BEFORE INFECTION	GROUP 2 ANIMALS TREATED WITH THYROXIN SIMULTANEOUSLY WITH INFECTION
	<i>Number of deaths</i>	<i>Number of deaths</i>
1st	—	2
2nd	—	3
3rd	—	6
4th	3	8
5th	4	8
6th	5	8
7th	9	8
8th	10	10
9th	10	

DISCUSSION

From the experimental point of view the thyroid gland undoubtedly exerts an influence on the development of tuberculosis.

Thyroid deficiency shortens the survival time of tuberculous animals, as compared with that of the controls. This difference becomes evident during the first months after infection, in which period deaths were more frequent among thyroidectomized guinea pigs. At autopsy only a few specific lesions were found in these animals. The guinea pigs in which hyperthyroidism had been provoked by thyroxin injections were more resistant against tuberculosis and died later. The longer survival period of these animals permitted the development of specific nodules in accordance with the greater effectivity of the immuno-biological forces of defense.

The results obtained seem reasonable if the rôle played by the thyroid gland in the mechanism of immunity is borne in mind. In his experiments on dogs and rabbits, Fassin (1907) found that thyroidin injections were likely to increase the hemolytic and bactericidal alexins of the serum, whereas the removal of the thyroid gland brought about a noticeable decrease of alexins. Variations of the same nature were reported by Marbé (1908, 1909) with regard to the opsonic index and to the phagocytic activity of the leucocytes in animals treated with thyroid extracts and in thyroidectomized animals.

These results were confirmed by Ascher (1924), who observed a decrease of the micro- and macrophagocytic activity in thyroidectomized animals. Goldzieher

and Hirschhorn (1927) found an increased activity of the reticulo-endothelial system in animals with artificial hyperthyroidism provoked by thyroxin injections. This should bring about an increase of their resistance to tuberculosis.

These observations provide an explanation for the susceptibility to tuberculosis of myxedematous patients, and for the increased resistance to this illness of patients with hyperthyroidism.

Thyroxin treatment, even in doses that are likely to cause a certain degree of hyperthyroidism in tuberculous patients, if controlled by determinations of the basal metabolic rate, could be tried; for the increase of the immunity mechanisms in these patients seems likely to bring about favorable effects.

SUMMARY

1. Removal of the thyroid gland in guinea pigs causes a greater susceptibility to experimental tuberculosis.

2. Thyroxin injections administered before or simultaneously with inoculation of tubercle bacilli prolong the period of survival of guinea pigs.

3. The greater resistance to tuberculosis of animals with hyperthyroidism might be due to increased immunity, attributable to the effects of the glandular secretions.

SUMARIO

1. La extirpación de las glándulas tiroideas en los cobayos determina una mayor susceptibilidad a la infección tuberculosa experimental.

2. Las inyecciones de tiroxina, iniciadas previamente o al mismo tiempo que la inoculación tuberculosa, alargan la supervivencia de los cobayos.

3. La mayor resistencia a la tuberculosis de los animales hipertiroideos sería debida al aumento de los procesos de inmunidad que determinan los productos de secreción tiroidea.

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ACID-PERMANGANATE MIXTURE FOR CLEANING GLASSWARE CONTAMINATED WITH TUBERCLE BACILLI¹

HORACE GOLDIE

Adequate cleaning of laboratory glassware contaminated with tubercle bacilli must satisfy the following requirements: (1) the material adhering to the glass must be entirely removed, while the glass should retain its original smooth surface and transparency; (2) the procedure should not leave any detectable traces of the cleaning fluid on the glass; (3) the substance should not be harmful to the workers under normal conditions of use; (4) the treatment should result in complete destruction of tubercle bacilli, even when present in large numbers.

Several widely used cleaning agents, soap, nitric acid, combination of sodium triphosphate, sodium silicate and sodium metaphosphate, etc., are believed to satisfy the three first requirements, but only the sulfuric acid-dichromate mixture is considered to be efficient enough for destruction of tubercle bacilli. This agent is highly irritating not only to the skin (which is usually protected by rubber gloves) but also to respiratory organs and eyes which can be effectively protected only by cumbersome special masks and goggles. The dangers of this fluid have been repeatedly emphasized in text-books (1, 2). Moreover, Henry and Smith (3) have concluded, as a result of their careful chemical investigation, that "because of the extreme difficulty in ridding glassware of dichromate after cleaning in cleaning solution and its great toxicity for living cells and enzymes, it is believed highly advisable in laboratories dealing with such materials to clean glassware by another method, such as 10 per cent nitric acid, a detergent, or 1 to 5 per cent trisodium phosphate." Unfortunately these agents do not destroy tubercle bacilli.

The cleaning action of acid-dichromate mixture is attributed to its high oxidizing power. As a substitute we used a solution of potassium permanganate in sulfuric acid developing the permanganic anhydrid Mn_2O_7 ($2\text{KMnO}_4 \div 2\text{H}_2\text{SO}_4 = 2\text{KHSO}_4 \div \text{Mn}_2\text{O}_7 \div \text{H}_2\text{O}$) which is "the most powerful oxidizing agent setting fire to the most combustible bodies" (4).

The mixture is prepared by dissolving 50 g. of potassium permanganate in 5 liters water and slowly adding to this solution 50 cc. of commercial sulfuric acid. After an exposure to this mixture overnight, the glassware is transferred to a solution of 120 g. oxalic acid in 5 liters hot water.

The oxalic acid solution is allowed to cool under frequent stirring and the glassware is left in this solution overnight; next day it is rinsed by running tap water for half an hour; the permanganate compounds are decomposed by oxalic acid and washed completely out of the glassware with the excess of oxalic acid, by running tap water.

For experimental testing of the cleaning fluid, heavy suspensions of human tubercle bacilli were suspended in 10 cc. physiological salt solution and amounts

¹ From the Bureau of Laboratories, City of New York Department of Health, 125 Worth Street, New York 13, New York.

of 1 cc. of suspension were placed in 50 cc. centrifuge tubes, 40 cc. of cleaning fluid added, the tubes shaken and left overnight; the next day they were centrifuged, the supernatant fluid poured off and replaced by the oxalic acid solution, the tubes were shaken again, left overnight and centrifuged. The precipitated material was smeared, stained and examined; no bacterial structures and no acid-resistant debris were found in the smears.

For testing the value of the acid-permanganate method in cleaning glassware contaminated with sputum containing tubercle bacilli, centrifuge tubes containing 1 to 5 cc. of heavily contaminated sputum were immersed in acid-permanganate solution and left overnight. The tubes were then transferred to hot oxalic acid solution, left overnight, rinsed in running tap water and dried. Smears were obtained by rubbing the inner surface of the tubes with the end of a soda straw and suspending any material so obtained in a few drops of physiological salt solution and egg albumin solution.

Eighty new tubes containing bacilliferous sputum were cleaned by the described method. No acid-fast bacilli were found in smears from these tubes after cleaning. Tuberculosis sputum was also introduced into 55 old centrifuge tubes which showed scratches on their inner surface as a result of cleaning with brushes. The latter tubes were cleaned in the same manner. Two of these tubes showed acid-fast bacilli in smears made from the tubes after cleaning. After the first test the tubes were dried and rubbed again with the moist straw; the obtained suspension was smeared on the slides. Careful examination of repeated smears from all those tubes failed to show acid-fast bacilli. The fact that none of the reexamined 53 negative tubes has shown positive results on reexamination, while the 2 positive tubes became negative on reexamination, suggests that negative results were not accidental, while the 2 positive results were due to the poor condition of the inner glass surface.

Chemical cleaning with acid-permanganate appears adequate to destroy tubercle bacilli in tubes with smooth inner surface. Old tubes with rough or scratched inner surface may be made safe for receiving new specimens if the chemical cleaning is followed by mild mechanical cleaning.

As a control method we used an alkaline permanganate solution (125 g. commercial lye and 50 g. potassium permanganate in 5 liters) in the same way as the acid-permanganate fluid; the glassware was cleaned effectively but acid-fast material was not destroyed.

The acid-permanganate fluid is, of course, irritating to the skin but to a lesser degree than the acid-dichromate mixture; its use does not affect the eyes or the respiratory tract of the worker, and does not require any special precautions.

The cleaned glassware appeared to remain after use in the same condition as before cleaning; no deterioration, mechanical or chemical, and no traces of cleaning fluid could be detected.

This method appears to satisfy the four requirements for adequate cleaning as formulated in the introduction to this paper.

CONCLUSIONS

1. An oxidizer-sulfuric acid chromic fluid is potentially dangerous for the skin eyes and respiratory tract of exposed persons.

2. Of the two oxidizing solutions of potassium-permanganate, the acid solution and the alkaline solution, only the acid solution satisfactorily destroyed tubercle bacilli in heavily contaminated glassware.

3. The fact that no "negative tubes" became positive on reexamination, while the two "positive tubes" became negative suggests that the negative results were not accidental, and that the two positive results were due to the cracks on the glass surface.

4. The acid potassium-permanganate method is perfectly adequate for cleaning new tubes and its combination with a mild mechanical cleaning (rubbing with a cotton applicator) is efficient for the cleaning of scratched tubes.

5. The acid potassium-permanganate fluid does not release any toxic gas compounds, has no smell and is not corrosive for the skin on short contact. It does not affect the glass and its cost is relatively low.

CONCLUSIONES

Limpieza de la Cristalería Contaminada con Bacilos Tuberculosos

1. Una mezcla de oxidante y ácidos sulfúrico y crómico es potencialmente peligrosa para la piel, ojos y aparato respiratorio de las personas expuestas a la misma.

2. De dos soluciones oxidantes, una ácida y una alcalina, de permanganato potásico, la ácida fué la única que destruyó en forma satisfactoria los bacilos tuberculosos en la cristalería muy contaminada.

3. El hecho de que ningún "tubo negativo" se volviera positivo al ser reexaminado, en tanto que los dos tubos "positivos" se volvieron negativos indica que el resultado negativo no fué puro accidente, mientras que los dos resultados positivos se debieron a grietas en la superficie del vidrio.

4. La técnica del ácido-permanganato potásico es absolutamente adecuada para limpiar tubos nuevos, y combinada con una leve limpieza mecánica (fricción con un aplicador de algodón) resulta eficaz para la limpieza de tubos rayados.

5. La mezcla líquida de ácido-permanganato potásico no libera compuestos gaseosos tóxicos, es inodora y no resulta corrosiva para la piel en un breve contacto. Tampoco ataca el vidrio y es relativamente poco costosa.

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EDITORIAL

Management of Minimal Tuberculosis

During recent months the Tuberculosis Control Division of the United States Public Health Service has issued a number of informative and challenging articles and editorials¹ on various aspects and problems related to the control of tuberculosis in this country. Particular consideration is given to the classification, disposition and treatment of persons found in X-ray surveys to have lesions in the chest, a problem of growing importance since this type of survey is being applied on a widening scale. It is generally agreed that a proportion of these cases represent tuberculous lesions which spontaneously have become arrested or healed and need no active care except perhaps for periodic reexamination. There are also the advanced and cavitory cases of tuberculosis for which, as a rule, institutional care is obviously indicated. A much larger group of cases of less certain status require careful and elaborate clinical evaluation of their potentialities and need of treatment. A shortage of hospital beds for the tuberculous, which Hilleboe estimates to be 50,000 for the country, compels some present compromises in dealing with the problem. But, while preoccupied with this necessity, we should not be diverted from determining the best ultimate solutions and asking for the machinery to implement them. The newly established Tuberculosis Control Division has made a good start toward promoting and supporting antituberculosis work in various parts of the country and is sufficiently young, elastic and responsive to profit by a discussion of some of its developing policies.

Hilleboe, formerly the director of the Tuberculosis Control Division and now an Assistant Surgeon General, enunciates the policy that "The protection of the health of the community takes precedence over the health of any individual." This is, on its surface, a realistic and accepted principle of public health practice, but warrants some critical analysis because it seems to carry the abhorrent implication that some tuberculous patients may be denied a chance to recover because the general welfare takes precedence. There should never be the necessity for such an unhappy choice and an informed community could and should be persuaded to remove the necessity if and where it exists. On this assumption, what principles can be accepted as basically sound for the proper disposition of discovered cases?

There will hardly be disagreement about the necessity of providing institutional care for the person with cavitory and infectious tuberculosis as a humane act and a means of safeguarding the community. However, there has been and will

¹ Among those of particular interest are the following: H. E. HILLEBOE: What is early tuberculosis, Pub. Health Rep., September 6, 1946, 61, 1295; Controversial issues in tuberculosis control, Pub. Health Rep., November 1, 1946, 61, 1561; The general practitioner in tuberculosis control, Pub. Health Rep., December 6, 1946, 61, 1757. H. E. HILLEBOE AND J. HOLM: Guide for disposition of persons with abnormal pulmonary findings on X-ray films, Pub. Health Rep., December 6, 1946, 61, 1759. H. E. HILLEBOE: Economy of bed usage in tuberculosis, Pub. Health Rep., February 7, 1947, 62, 185.

continue to be a good deal of protest against the concepts proposed by Hilleboe with regard to the patient with "minimal pulmonary tuberculosis." The fundamental issue here is whether or not the lesion is likely to progress into advanced, disabling and grossly infectious disease if treatment is not given. While it is known that advanced and fatal tuberculosis usually has its recognizable inception in a single small lesion in one lung, there is still disagreement about the meaning of a small lesion when it is first discovered. Hilleboe takes the rather extreme position that no lesion should be diagnosed definitely as tuberculous until it is known that the patient reacts to tuberculin and tubercle bacilli can be demonstrated in the sputum or gastric washings. The first criterion is generally accepted but the second implies that a diagnosis should not be made until the lesion has become caseous and necrotic and has started to discharge its purulent contents into the bronchial tree. Further, it implies a diminished prospect of cure, since there is accumulating evidence that the breakdown and ulceration of a tuberculous lesion is almost always associated with some increase of the disease through intrabronchial spread of the infection; also the disease is now definitely communicable. In actual practice, tubercle bacilli are usually not demonstrated until destruction and excavation of the lung has progressed well beyond a small ulcerative process, a misfortune which is traced, not only to inadequate laboratory technique, but also to the difficulties of obtaining proper specimens of sputum or gastric contents. While Hilleboe states that "The minimal case with laboratory and other evidence of active disease should be given equal opportunity with the advanced remediable case, so that progression of disease can be prevented," he also contends that "there is yet no evidence in medical literature that the minimal lesion with negative sputum, negative gastric lavage, or no sputum, is benefited by sanatorium care." This may be true of the old fibroid "minimal" but few, if any, experienced clinicians will accept it for a lesion of the same extent but vastly different in its pathological morphology (that is, exudative, lobular pneumonic and caseous) and in its implications especially for adolescent and young adult patients. More often than not, in the early course of the progressive small pneumonic infiltrate all alleged activity tests are negative; and this is especially true of attempts to demonstrate tubercle bacilli, unless many specimens are examined with particular care.² Yet here, before irreparable destruction has occurred, is the rarest of all opportunities to prevent advanced and grossly infectious disease. For the good of the individuals as well as that of the community such patients have a claim

² Since Doctor Hilleboe fails to stress the importance of frequently repeated examinations of suitable specimens, it should be pointed out that, for example, Dr. Wm. P. Swisher, in a paper recently published in the REVIEW (June, 1947), reports that, in discharged soldiers with positive bacteriological findings, over 56 per cent of all cases and 68 per cent of minimal cases had 3 negative specimens before acid-fast bacilli could be identified, and that in 61 patients from 5 to 14 negative results preceded the first positive finding; and Abeles and Pinner (Am. Rev. Tuberc., 1944, 49, 490) found tubercle bacilli in accidentally discovered cases of pulmonary tuberculosis on first examination after hospitalization in only 32 out of 77 cases, and that in 26 patients a total of 59 negative cultures (sputum and gastric) were made before a positive result was obtained. [Editor]

for prompt, even if presumptive, diagnosis and immediate institutional treatment or its equivalent which equals or transcends that of the patient with manifestly cavitary disease. The real task is to discriminate between the patient with "minimal" fibroid and with "minimal" pneumonic tuberculosis and the various gradations of these. For this there is no easy method. Careful, sometimes prolonged observation, repeated meticulous examinations and the best clinical judgment are required. A good hospital or sanatorium is usually most suitable for the purpose. Sufficient evidence is developing that this is usually efficacious in making proper distinctions between cases and in arresting early tuberculosis. It seems to be the only way of using institutional beds to better advantage. To-day, in spite of much furor about finding early cases, most sanatoria are crowded with patients whose tuberculosis is so advanced that little can be promised them save palliation.

Usually there is little difference among public health officials and clinicians when, together, they face these issues with the individual patient. The need is for a closer meeting of the minds in developing broad policies and particularly in laying plans for the future. The *Guide for Disposition of Persons with Abnormal Findings on X-ray Films*, devised in the Public Health Service, is "provisional" and presumably will be modified. Its chief defect is its failure to follow recent thought about early "minimal" tuberculous lesions, and it seems reasonable to suggest that this be corrected before the *Guide* becomes a fixed policy.

J. BURNS AMBERSON

BOOKS

LEO G. RIGLER: *The Chest—A Handbook of Roentgen Diagnosis*. Pp. 352, with 338 illustrations, The Year Book Publishers, Inc., Chicago, 1946, cloth, \$6.50.

By L. HENRY GARLAND

This is one of the series of monographs published by the Year Book Publishers of Chicago. In this reviewer's opinion, it is one of the best to date. The author deals in a thorough and systematic fashion with the technique and methods of roentgen diagnosis of pulmonary disorders.

On the controversial question of the roentgen findings in so-called first infection tuberculosis in children, he uses the phrase "characteristic" for findings which are really nonspecific. As far as reinfection tuberculosis is concerned, this reviewer would like to see greater emphasis on the fact that the diagnosis of tuberculosis cannot be made from a roentgenogram! It requires bacteriological evidence. The roentgen term should be "inflammatory disease," with, if the interpreter wishes, the phrase "presumably tuberculous" added.

The remarks on sarcoidosis are rather terse. The predilection for involvement of the right paratracheal lymph node chain might have been stressed.

The text is highly legible; the illustrations are in general beyond reproach, despite their small size (mostly about three inches square). The book can be heartily recommended to students, practitioners and especially to physicians interested in pulmonary disorders.

MOSES J. STONE AND PAUL DFAULT: *The Diagnosis and Treatment of Pulmonary Tuberculosis*. Pp. 525, Lea & Febiger, Philadelphia, 1946, cloth, \$3.50.

By CHESLEY BUSH

This book, which is a successor to Hawes and Stone's little volume on the same subject, is a completely revised edition. It is entirely rewritten, as demonstrated by a careful comparison by this reviewer, and contains much additional material. Its size has been increased by over one hundred pages. Entire new chapters on the pathology and bacteriology of tuberculosis have been added, which incorporate on the whole the modern concept of phthysiogenesis and pathology. Its brevity is still pronounced, and it may best be described as an epitome or digest of tuberculosis from a medical standpoint. It is a valuable handbook for the medical student or general practitioner who desires a brief review of the subject. Each chapter is well documented for those who wish to go further.

The knowledge of diseases of the chest in general and tuberculosis in particular is advancing so rapidly these days that it becomes increasingly difficult to find a text-book which is entirely up-to-date. This book illustrates this point well. In the chapter on differential diagnosis, histoplasmosis is not mentioned. The chapters concerning artificial pneumothorax deal with pneumoperitoneum

solely as an accident or a complication of pneumothorax, due to faulty technique. It is not mentioned as a form of collapse therapy which is rapidly gaining favor in many parts of the country. Insufficient emphasis is placed on the importance of adequate pneumothorax and of prompt abandonment of this therapy if it proves inadequate and adhesions are not controllable. In the chapter on *Attempts at Special Therapy*, the newer antibiotics are not mentioned.

The chapters are well balanced on the whole; still, three pages on rest out of one hundred seven on therapy seem to place insufficient emphasis on rest, which still is the basis of all treatment of pulmonary tuberculosis.

We are continually being asked by lay-patients and lay-workers for an authoritative book on tuberculosis. This book will meet the demand for those with a medical background, but hardly for those without. The fact is that any work purporting to give the modern concept of tuberculosis and its therapy has a very short time of being up-to-date, and is likely to fall by the wayside unless it is solidly based on the fundamentals which have changed very little. If the fundamentals are adapted to the newer therapeutic methods, a well rounded work will result. This the authors have achieved within the limits which they have set themselves.

GERALD B. WEBB AND DESMOND POWELL: *Henry Sewall, Physiologist and Physician*. Pp. ix + 191, Baltimore, The Johns Hopkins Press, 1946, cloth, \$2.75.

By SIDNEY J. SHIPMAN

This excellent biography will be especially appreciated by the older generation of chest specialists, particularly by those who have had the opportunity to know and therefore admire Dr. Henry Sewall. The book is extremely readable. There are many touches which can be recognized as those of Dr. Gerald Webb.

It is not necessary, however, to be an elder statesman or to have known Doctor Sewall personally to enjoy this biography. The account of Doctor Sewall's early battle with tuberculosis is naturally of interest to students of the disease. As a young man, we are told, Sewall was never strong and during his early college days at Wesleyan he developed his first attack of pleurisy. Unrecognized for what it was—the onset of his tuberculosis—it did not prevent him from inaugurating the science course at the University from which he was graduated. He was the first student to receive the B. S. degree.

Sewall was a part of the early Johns Hopkins University. Professor Henry Martin, then 28 years of age, employed Sewall at a salary of \$250.00 for six months. This was the period during which the conflict between religious and scientific ideas was at its height and Sewall, coming of a long line of religious people, manifested many of the emotional conflicts of his age. The physiologist and the experimenter were nonetheless uppermost in his make-up. In 1879 he went abroad, studying under the famous physiologist, Carl Ludwig of Leipzig. During the same year, under Sir Michael Foster, he worked on the pepsin-

forming glands. In 1880 he returned to Johns Hopkins where he was made assistant in physiology.

Since Victor Vaughan, Professor of Physiological Chemistry at the University of Michigan, recognized Sewall's unusual gifts and capacities, he called him to the University of Michigan to take the chair of physiology in 1882. Here he had as his first students such famous men as F. P. Mall, William J. Mayo and Walter Courtney. Frederick Novy studied physiology under Sewall. In turn, Sewall was later to study bacteriology under Novy, and in his laboratory he examined and found tubercle bacilli in his own sputum.

From 1884 Sewall was afflicted with clinical tuberculosis. Meanwhile, however, at the University of Michigan he pursued his classic work on immunization with snake venom, establishing his rarely acknowledged priority as discoverer of antitoxic immunization. A fairly detailed account of this is given in Sewall's own words, perhaps his outstanding contribution. At any rate, it is probable, according to Webb and Powell, that Sewall's snake venom experiments inspired the development of immunization in diphtheria.

In spite of ill health, Sewall was married to Isabel Vickers of Toronto, Canada on September 21, 1887, two years before he discovered tubercle bacilli in his sputum. This marriage was the result of a meeting brought about by the Victor Vaughans of the University of Michigan. Although the marriage was to last fifty years, it was not long afterward that Sewall was obliged to seek refuge in Colorado because of its supposed beneficial climate. He did not take the "cure" in the modern sense, however, preparing for his M. D. degree which was granted him in 1889 at Denver. Following this, Sewall was given the position as resident physician at Saranac Lake through the intervention of Doctor Welch and Doctor Trudeau, an act that, as he says, "saved his life." Interestingly enough, however, Sewall and Trudeau never got on well together. Both were somewhat irascible gentlemen at times. Yet it is possible that Sewall stimulated Doctor Trudeau in some of his earliest work. Be that as it may, the association was one which could not last and Sewall was, therefore, not disinclined to listen to Dr. Samuel Fiske when the latter asked him to return to Colorado. This time Sewall engaged in private practice and became associated with the Board of Health. He also began lecturing in physiology at the Medical School. Always active in tuberculosis work, he took part in the founding of the National Association for the Study and Prevention of Tuberculosis in Atlantic City in 1904. Later, in 1931, he was to receive the Trudeau Medal from the National Tuberculosis Association for his distinguished work in tuberculosis. He served as president of this Association in 1927.

Sewall's interests were not limited to tuberculosis and physiology. He took an active interest in the affairs of the Colorado State Medical Society and, in 1923, became president of that organization. From 1911 to 1918 he served as Professor of Medicine at the University of Colorado Medical School. His work has been admirably summed up by Dr. Florence Sabin, who, in giving the Henry Sewall lecture on May 28, 1937, said, "Sewall's work with Kuhne on the eye; his discovery that a stimulus not of itself strong enough to cause a

reaction nevertheless modifies the reaction to succeeding stimuli; his determination of the function of the depressor nerve, for which Howell had so great an admiration; his work on immunity to snake venom; his independent studies at Saranac (in which he compared the form and staining characteristics of various strains of tubercle bacilli) which are in agreement with the most advanced bacteriology of today; his studies on the heart; his numerous papers on tuberculosis, especially those which were concerned with the relationship between immunization and sensitization."

One of the most noteworthy chapters of the book is the chapter devoted to letters. Here are several interesting communications between Sewall and Allen K. Krause, as well as a number of other well known persons in the tuberculosis field.

To your reviewer it is a matter of gratification that, although Sewall went to Denver for his health and extolled the climate of Colorado, he was wise enough for many years to spend his winters at La Jolla, California.

Rehabilitation of the Tuberculous. Proceedings of the Conference on the Rehabilitation of the Tuberculous, sponsored by The Office of Vocational Rehabilitation, Federal Security Agency, and The Tuberculosis Control Division, U. S. Public Health Service, Federal Security Agency, and The National Tuberculosis Association, March 4-6, 1946, Washington, D. C. Edited by Holland Hudson and Norvin C. Kiefer. Pp. ix + 138, published by the National Tuberculosis Association, 1790 Broadway, New York 19, N. Y., 1946, paper, \$2.00.

By LOUIS E. SILTZBACH

The press, radio and recently the films have been educating the public to the need for restoring to fitness the many who are physically handicapped, particularly those whose disabilities are due to the war. Last fall the President signed a bill authorizing the observance of "Employ the Physically Handicapped Week." The Secretary of Labor reported that during the first twenty days of that month employment of the handicapped increased 35 per cent over the same period of the previous month. Attention has been focused, naturally enough, on persons having visible defects, such as those of limb and eye. Although the tuberculous have not had this publicity, they are sharing in the revival of interest in what has recently been called the third phase of medical management—rehabilitation.

In March, 1946, the Office of Vocational Rehabilitation, the Tuberculosis Control Division of the U. S. Public Health Service and the National Tuberculosis Association jointly sponsored a three-day conference in Washington on the rehabilitation of the tuberculous.

This 138-page booklet is a condensation of the proceedings. The participants included clinicians and public health physicians, institutional and public health nurses, medical social workers, rehabilitation counselors, occupational therapists, educational advisors and statisticians—all experienced in the field of tuberculosis.

Throughout the text, like a scarlet thread, runs the well-taken thesis that the rehabilitation movement needs team effort; that for each professional group there is a well-defined area wherein they can be of greatest usefulness, and only by absorbing the principles which underlie the others' efforts can they see their own tasks more plainly. In reading these pages one senses that—at long last—the various professional groups are getting properly introduced and perhaps are even beginning to talk the same language.

Academic training and experience requirements for personnel were discussed in detail. A set of clear-cut standards emerges, which is bound to give new impetus to the whole rehabilitation effort. For it has been shown time and again that lack of properly qualified personnel can cripple social welfare projects.

The discussion of the medical aspects of rehabilitation—unfortunately, too brief—will be of particular interest to the physician. The terms *fully rehabilitated*, *partially rehabilitated*, and *not rehabilitated* are defined, using work tolerance as a basis. The first term, for example, is applied to patients who are "able to work 40 hours a week without any evidence of a tendency toward a breakdown either physical, mental, emotional or otherwise;" and the second, to those able to work twenty hours or more with the same qualification. It strikes this reviewer that it might be difficult to get two physicians to agree upon what constitutes a "tendency" toward a physical breakdown. Predicting a relapse in a patient who meets the criteria for arrest is still pretty much an uncertain business. Symptoms which might be considered as precursors of a recurrence have generally proved to be the expression of the recurrence itself. The qualification in the definition is intended no doubt to indicate that the patient can function for the hours specified without undue fatigue or deterioration of the general condition.

A rehabilitation classification with several sections sets forth graded activity prescriptions at the sanatorium, the patient's work capacity and infectiousness at the time of his discharge from a sanatorium, and the prognosis for eventual return to everyday employment. The prognoses are designated good, fair, questionable or poor.

With this classification, the physician is enabled to inform the rehabilitating agency that a given patient, for example, is noninfectious, that he can work four hours daily for a total of twenty hours a week at a suitable job and that his prognosis for recovery of full work-capacity is good. Generally, the rehabilitation agency will require, in addition, a rough estimate of the proposed length of the course. For that purpose, this reviewer assesses the patient's clinical course and activity program at the sanatorium, and places him in one of three categories which follow: (1) six months to one year; (2) more than one year; (3) permanent sheltered employment.

These are necessarily tentative groupings. But with proper follow-up observations, the clinician can learn to slot the patients fairly accurately. Few patients discharged from sanatoria with arrested disease require a rehabilitation course of longer than one year. For the general run of such patients, the minimum course comes to about half as long a time as he passed in the sanatorium.

The conference again pointed up the need for control studies to assess the

value of rehabilitation in tuberculosis in general, and to compare the results achieved by the various schemes now operating. The participants were perhaps unduly concerned with the necessity of obtaining truly matched groups of patients who have, and have not, had the benefit of formal rehabilitation services. Such groups would have to be comparable with respect to age, sex, stage of disease, sputum history, clinical status, length and method of treatment, socioeconomic, psychic and educational background. One is reminded of the controversies which raged not so long ago around the question of the value of the sanatorium in the treatment of tuberculosis.

But the truth is, in such multifactoral situations, that it would be impossible to give completely accurate weight to each factor, even if we had the data. On the other hand, there is much to be gained from the study of roughly matched groups, particularly when they have been subjected to adequate follow-up observation. There is undoubtedly considerable material worth study in the files of state rehabilitation offices. The timely publication of the results achieved in terms of successful post-sanatorium readjustments and recurrence rates would be enormously helpful in the present stage of planning and expansion.

All who took part in the conference expressed their belief in the value of rehabilitation. For the writer, this feeling is fortified by the satisfactory life-expectancy experiences and recurrence rates reported by some of our functioning rehabilitation organizations.

The conference was for the most part exploratory. But already the rehabilitation programs of six tuberculosis institutions have been studied by a team composed of members of the various before-mentioned specialties. The logical next step is to study post-sanatorium problems—a subject that presumably will be high on the agenda of a second conference which is planned for 1948.

The editors of this booklet, Mr. Holland Hudson, Director of the Rehabilitation Service of the National Tuberculosis Association, and Dr. Norvin C. Keifer of the Federal Tuberculosis Control Division, have done an expert job. Their text gives one a sense of being present at the conference and listening.

Medical Social Service in Tuberculosis Control. Miscellaneous Publication 57, Federal Security Agency, United States Public Health Service, 1946. Forewords by Thomas Parran and Herman E. Hilleboe.

By W. H. OATWAY, Jr.

Publication #37 is an unusually complete and satisfactory description of the function of social service in a program for control of tuberculosis.

Doctor Hilleboe has sketched the problem, mentioned a proposed plan of the U. S. P. H. S. for a medical social service and described the formation of an advisory committee of social workers. The Committee has defined the functions of a medical social service worker, both broadly and in detail, in relation to a tuberculosis control program.

Tuberculosis, the tuberculous patient, and the family of the patient are briefly analyzed and then correlated with the optimal methods of social service.

A review of the section headings is revealing; Evaluation of the Problem; Research and Health Education (including a list of approved schools of social work); Case-finding; Medical Care, Isolation and After-Care; Rehabilitation; Protection against Economic Distress. The bulletin is inclusive, but the description is both concise and catalogued.

The position of the social service worker is definitely on a level with the physician in this scheme. Probably, during the often lengthy duration of an illness, they should be rated together.

The report strongly favors an increase in assistance, relief or insurance, to provide an economic security for the patient and his family. The program would be too ambitious and dreamy-eyed for reality, were it not for its logic, its need and the potentialities of the United States Public Health Service.

O. GENGOU: *L'endémie tuberculeuse et sa prophylaxie*. Pp. 420, *Ligue Nationale Belge contre la Tuberculose*, Rue de la Concorde, 56, Bruxelles, 1945, paper.

By GEORGE WOLFF

This elaborate work is a valuable contribution to tuberculosis epidemiology and the practical campaign against the disease. It is especially valuable to the student in this country because the French and German literature during the last two decades is amply used besides English and American publications. The subject matter is divided into three large parts dealing with biological-etiological and social-pathological factors in the first part (*L'endémie tuberculeuse*), the principles of isolation and immunization in the present fight against tuberculosis in the second part (*Principes et méthodes de prophylaxie antituberculeuse*), and finally with the organization of the tuberculosis campaign (*Organisation de la prophylaxie antituberculeuse*). In the latter parts such items as the famous *Oeuvre Grancher*, created in France and providing the removal of the new-born from his tuberculous parents or other tuberculous sources in the family, are given special consideration together with the establishment and equipment of preventoria and sanatoria, public education and legislation in Belgium. A detailed chapter is further devoted to the application of prophylactic vaccination (BCG) all over the world. Relatively little attention is given to the part heredity may play in the evolution of tuberculosis in families (twin research, etc.). A large bibliography covers over 700 items, directly or indirectly quoted in the text. A few repetitions occur in the second and third main part, the sub-chapters of which do not fully exclude each other. But, all in all, the description and discussion of the major topics is well organized, which perhaps could still be improved by a subject-index.

One critical remark must be made. When the author deals with statistics—and in epidemiological discussion he has to—he is not always felicitous in select-

ing, describing and interpreting the sources. First of all, most tables and diagrams produced in the epidemiological section (especially chapter VII, pp. 94-128) have no or no accurate legend or heading; one must, therefore go back to the text and find out what is meant. Of course, the author is no statistician, and he need not be for his work; but he quotes statistics quite extensively and bases his conclusions on them. There are some minor errors, even in the presentation of tables from other sources; for instance on page 68, where the death rates from tuberculosis in Saxonia, Prussia and Bavaria, 1914-1918, are contrasted to show the influence of the degree of industrialization upon tuberculosis in single countries. All these rates are given as per cent (%) instead of per 10,000, while in the text the mortality *change* is correctly expressed in percentage. Such inaccuracies occur repeatedly in the quoted material (for instance, on pages 90, 122/23, etc.). However, these are minor errors of technique. Of more importance is the fact that, in the detailed chapter dealing with BCG (chapter XVII: *La prémunition*, pp. 254-289), the author quotes a number of statistics favorable to the effect of BCG, but he almost entirely leaves out the unfavorable ones. Protests against some of the former statistics were made by professional statisticians of reputation (Greenwood, London; Rosenfeld, Vienna). Clinicians should be aware that selection of controls in statistics plays a rôle, as important as in experiments, that must not be underestimated. To make the comparison in homogeneous groups (as far as possible) is one of the fundamental logical laws in statistics, and particularly in statistical methods. The evaluation of the efficacy of BCG vaccination is, in this reviewer's opinion, not yet completely certain, though it may be possible to reach absolute proof. But so far, it is a fact that in some countries where BCG vaccination has been amply used (France, Roumania) tuberculosis mortality is not especially low nor has it been unusually lowered since its introduction.

ANNA M. BAETJER: *Women in Industry. Their Health and Efficiency. Issued under the auspices of the Division of Medical Sciences and the Division of Engineering and Industrial Research of the National Research Council. Prepared in the Army Industrial Hygiene Laboratory. Pp. xi + 344, with 122 tables and 35 figures, W. B. Saunders Company, Philadelphia and London, 1946, cloth, \$4.00.*

By ETHEL D. OWEN

This is a small volume of 344 pages. It deals with the problems of women in industry from a somewhat new standpoint.

More women have been employed in heavy industry during the war period both in the United States and Britain than ever before in the history of either nation. The urgent need in war of employing all workers to produce with maximum efficiency was of paramount importance. The author stresses the need for adapting the woman to the work to be performed, even if it means altering hours, machinery, etc.

The analysis of causes of absenteeism in women workers of all classes has been made with more intelligence and less prejudice than is usual in such evaluations. The fact that the efficiency of the woman worker is often sharply limited by home duties, such as care of the elderly, invalids, young children and shopping for the family, is recognized.

In the observations regarding illnesses and accidents, the conclusions are that women workers do not have accidents any more frequently than men employed in the same kind of work and that loss of time from work is in general due to illnesses common to both sexes. Upper respiratory infections during the winter months represent the single largest cause for loss of time due to illness.

Only in the case of pregnancy must there be any great modification of conditions. There are certain industries involving mechanical hazards and toxic materials which are not suitable for a pregnant woman.

Women report off duty more frequently than men but the length of time they lose is less. Men report off duty with more serious conditions than women workers. Mortality of males exceeds that of females at all ages and in some similar occupations. There may be some connection between these two facts.

Married women have more illness than single women, unemployed women more than the employed. The younger age groups represent less efficiency and more illness than the middle aged.

The average yearly tuberculosis mortality rate for 1931 to 1940, inclusive, was higher for men than women (all age groups), 56.5 as against 43.6 for respiratory forms; and 5.6 against 4.8 for "other forms" of tuberculosis. In other words, the rates for males were 29.6 and 16.7 per cent higher. Mortality rates for women were higher than for men for "cancer and other malignant tumors" by 15.6 per cent; for diabetes mellitus by 37.8 per cent; for exophthalmic goiter by 81.6 per cent; for biliary calculi by 57.7 per cent.

The book represents careful research. The author states that many observations may require modification and extension in the years to come during the more normal routine of peace.

Books Received

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F. DUMAREST, H. MOLLARD, P. LEFÈVRE AND J. GERMAIN: La pratique du pneumothorax thérapeutique. With Preface by F. Bezancon. Cinquième

- édition entièrement revue. Pp. 416, with 19 figures, Masson et Cie, Éditeurs, Libraires de l'Académie de Médecine, 120, Boulevard Saint-Germain, Paris VI, 1945, paper, 375 fr.
- G. S. ERWIN: *A Guide for the Tuberculous Patient*. American Edition revised and edited by Henry C. Sweany. Pp. ix + 126, Grune & Stratton, New York, 1946, board cover.
- WILLIAM SNOW MILLER: *The Lung*. Second Edition. Pp. xvi + 222, with 168 figures, Charles C Thomas—Publisher, Springfield, Illinois, 1947, vellum, \$7.50.
- J. SKLADAL: *Syndrome Cortico-Pleural. Son étude clinique et expérimentale*. Pp. 144, with 40 illustrations, Masson & Cie, Éditeurs, Libraires de l'Académie de Médecine, 120, Boulevard Saint-Germain, Paris, 1946, paper, 160 fr. (See book review in *Am. Rev. Tuberc.*, 1943, 48, 125.)
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- ERICH URBACH AND PHILIP M. GOTTLIEB: *Allergy*. Second Edition. Pp. xix + 968, with 412 figures and 64 tables, Grune & Stratton, New York, 1946, fabrikoid, \$12.00.
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- Handbook of Infectious Diseases. With Notes on Prophylaxis, Serum Treatment and Vaccination*. By the Staff of the Cantacuzène Institute, under the direction of Professors C. Ionescu-Mihaesti and M. Ciuca. Pp. 331 (pocket edition), Series of League of Nations Publications, III. Health, 1945, III, 1, Geneva, buckram, \$1.25.
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Pulmonary Schistosomiasis.—This is an abstract from a paper by H. B. Weinberg and A. J. Tillinghast, published in *Am. J. Trop. Med.*, November, 1946. Tubercle-like lesions were found in the lungs of 2 soldiers who had bathed in fresh water streams; both had ova of *Schistosoma japonicum* in their stools during the urticarial, pulmonary and febrile manifestations. The first soldier had a nonproductive cough and showed pulmonary infiltration on roentgen examination. He died suddenly; the autopsy revealed crepitant lungs studded with small, white, moderately firm nodules, varying in size from barely visible up to 2 mm. in diameter. Microscopically, the centre was necrotic with eosinophilic infiltration and surrounding fibrosis. In the centre of some of the nodules was an ovum of *Schistosoma japonicum* in various stages of degeneration. Similar nodules were found in the liver, mesenteric lymph nodes, rectosigmoid colon and appendix. The second soldier had a cough with a moderate amount of yellow mucoid sputum; roentgenograms showed miliary nodules. He recovered under treatment with tartar emetic. It was assumed that the pathological process was continuous and from the start a reaction to the localization of the ova in the tissues. This differs from textbook descriptions of the disease in which early pulmonary manifestations are said to be due to (1) the passage of cercaria through the pulmonary blood vessels, (2) allergic factors or (3) toxic effects.—*Pulmonary Manifestations Caused by Schistosoma Japonicum*, (not signed), *Bull. U. S. Army Med. Dept.*, November, 1946, 6: 505.—(O. Pin-ner)

Bronchopulmonary Geotrichosis.—*Geotrichum*, first described by Link in 1809, in many respects resembles *Blastomyces dermatitidis* and *Coccidioides immitis*. The genus is mostly saprophytic but infections have been reported in man. Smith has emphasized that patients with clinical symptoms of chronic bronchitis or pulmonary tuberculosis who have white mucoid sputum containing grayish flakes should be suspected of having an infection with *Geotrichum*. The organisms can be cultured on Sabouraud's media. A 22-year-old colored soldier, at one time stationed in Texas, developed chest pain, night sweats, weakness, productive cough and weight loss. Sputum examination revealed no tubercle bacilli or fungi and roentgenograms showed diffuse mottling throughout both lung fields. Sputum cultures revealed fungi of the genus *Geotrichum*. The pulmonary infiltrations cleared in three months on intravenous sodium iodide and oral potassium iodide.—*Bronchopulmonary Geotrichosis*, R. H. Kunstadter, R. C. Pendergrass & J. H. Schubert, *Am. J. M. Sc.*, May, 1946, 211: 583.—(G. F. Mitchell)

Pulmonary Torulosis.—Torulosis has been reported by a number of writers. Burger and Morton, on reviewing the literature, collected 100 cases to which they added 4. Lung involvement alone is rare, but patients with either central nervous system or generalized involvement often have pulmonary involvement. Roentgen findings are not characteristic, but they may suggest such a diagnosis. In a case reported by Swanson and Smith, which was seen in consultation with the au-

thors, the diagnosis was made from sputum studies and the pulmonary lesion showed regression after treatment. The case here reported is that of a 24-year-old WAC who developed pleuritic pain in July, 1943 and whose roentgenogram revealed a round opacity in the upper portion of the left lower lobe. The symptoms were mild and subsided on hospitalization. The girl's tuberculin test was negative. The blood count remained elevated though the patient was asymptomatic except for a mild cough for approximately six months. X-ray films at this time revealed multiple excavations. After potassium iodide was started in November, 1943, the patient developed chills and fever which persisted for eight days. Symptoms of central nervous system involvement occurred in January, 1944. *Tortula histolytica* was isolated from the spinal fluid. Potassium iodide produced some clearing of the chest lesions, but there was no clinical improvement. Sulfathiazole and penicillin had no effect and bacteriological assays of cultures made with sulfa drugs and penicillin revealed vigorous growth. A localized pleurisy, a circular hemorrhagic loculated lesion containing reddish-brown gelatinous necrotic material and irregular foci of gray consolidations resembling bronchopneumonia were found at autopsy. Circumscribed regions of complete loss of brain substance were found in the occipital lobe and mid-brain. The inflammatory reaction in both lungs and brain was slight. Torulosis frequently is seen as pulmonary lesions which often antedate central nervous system involvement. Since the pulmonary lesions are usually asymptomatic and may be found on routine examinations or because of mild symptoms, torulosis should be considered though tuberculosis may be suspected.—*Pulmonary Torulosis*, J. B. Hamilton & G. R. Tyler, *Radiology*, August, 1946, 47: 142.—(G. F. Mitchell)

Thresher's Lung.—This syndrome is described in 8 patients, all of whom had been exposed to the dust from mouldy ("burned") grain. It is believed to be caused by monilia, although it is pointed out that monilia is fre-

quently an insignificant saprophyte in the respiratory tract. The disease is characterized by a sudden onset with chill, fever, malaise, cough and mucopurulent or bloody expectoration. Dyspnea is the most important and persistent symptom. Fine bronchial râles are heard over the bases, a slight leucocytosis is usually present and the sedimentation rate is increased. Roentgenograms reveal pictures similar to miliary tuberculosis, but the fine mottling is densest in the parahilar regions and the bases, while the apices are relatively free. The X-ray signs may disappear or may result in patchy fibrosis with bronchiectasis. The disease is similar to, or identical with, the "tea taster's cough," as described by Castellani and the *Bronchomycosis feticisiorum*, as described by Fawcitt. Similarities with sarcoidosis are pointed out, particularly the negative tuberculin reaction, which remained negative even following BCG vaccination. Potassium iodide seemed to be of benefit, particularly in the milder cases. Ten excellent chest roentgenograms illustrate the roentgenological findings. The literature on dust inhalation and moniliasis is discussed.—*Thresher's Lung*, E. Tornell, *Acta med. Scandinav.*, 1946, 125: 191.—(M. Pinner)

Coccidioidomycosis.—The clinical features of the disease are discussed primarily from the standpoint of differentiating and specific characteristics which distinguish the disease from other acute and chronic pulmonary infections. The coccidioidin skin test has a high degree of specificity and parallels the tuberculin test in its mode of action. Precipitin and complement fixation tests have proved valuable, not only for diagnosis but also for prognosis. Ninety-six coccidioidal pulmonary infections which persisted for months or years following the acute initial phase of the disease are discussed according to predominant roentgen manifestations, as follows: (1) nodular parenchymal foci; (2) cyst-like cavities; (3) persistent pneumonitis; (4) mediastinal and hilar adenopathy; (5) pleural effusion; (6) miliary lung involvement, metastatic bone foci and other evidences of dissemination. The roent-

gen findings are correlated with associated clinical history. Twenty-three nodular and 35 cystic foci were shown to be extremely indolent, benign in character and slow in evolution. Twenty-one patients with persistent pneumonitis required hospitalization for many months. Mediastinal adenopathy was the predominant roentgen characteristic of 9 cases until the fatal miliary spread occurred. Factors which influence dissemination are discussed with emphasis on the racial factor. Negroes are about 100 times as likely to develop fatal disseminated coccidioidomycosis as white persons. White persons are more apt to develop a meningeal type of coccidioidal dissemination, while Negroes show a higher incidence of subcutaneous abscesses. Dissemination, when it occurs late, appears to be of less ominous prognostic significance than when occurring within the first few days or weeks of the initial acute illness.—(From the author's summary.)—*A Roentgen Study of Chronic Pulmonary Coccidioidomycosis*, H. W. Jamison, *Am. J. Roentgenol.*, April, 1946, 55: 396.—(P. Lowy)

Coccidioidomycosis.—A detailed epidemiological investigation of coccidioidomycosis was carried out in four Army air fields in the San Joaquin Valley, California. The investigation was based on coccidioidin testing permanent personnel and at first annually, later semi-annually, retesting the negative reactors. The pattern of geographic distribution of coccidioidal endemicity showed an increase in the southern part of the San Joaquin Valley with a decrease as one proceeds northward. Maximal incidence occurred in the arid dusty summer and autumn months. The seasonal infection rate showed that dust was the mechanism by which the fungus was transported. Grassing, paving roads and runways and ultimately the use of highly refined oil on athletic areas were important local dust control measures. This control reduced infection rates from one-half to two-thirds.—*Effect of Season and Dust Control on Coccidioidomycosis*, C. E. Smith, R. R. Beard, H. G. Rosen-

berger & E. G. Whiting, *J. A. M. A.*, December 7, 1946, 132: 833.—(H. Abeles)

Streptococcal Miliary Infiltrations of Lung.—The existence of an infiltration of lung tissue, giving rise to radiological shadows almost identical with those of pulmonary tuberculosis but not apparently connected with the tubercle bacillus, is well known. A case of an apparent acute streptococcal miliary infiltration of the lungs is described. A woman, aged 20, was admitted to the hospital, almost moribund, as a case of acute leukemia. She presented a picture of gross anemia and a virulent infection. She gave a history of increasing fatigue, weakness and pallor over the past two to three months. Immediately before admission, in addition to aggravation of these symptoms, she had noticed acute dyspnea on exertion, attacks of giddiness and palpitation, and a slight cough on the morning of admission. Seven weeks before the onset of this illness she had attended a mass radiography clinic, where her lung fields were reported as clear. On admission she was grossly anemic, too weak to cough and very "bubbly;" her respirations were shallow and rapid; the pulse was rapid and irregular; temperature 101°F. Chest examination showed scattered crepitations throughout both lung fields and bronchovesicular breath sounds. There was no lymphadenopathy or splenomegaly. X-ray examination of the chest showed diffuse miliary infiltration of all zones of both lungs but the apices were singularly clear. Repeated examination of the sputum (laryngeal mirror) showed an almost pure growth of hemolytic streptococci but no tubercle bacilli. Blood transfusions, penicillin, one million units in six days, and supportive therapy resulted in complete subsidence of symptoms. Serial X-ray examinations of the chest showed progressive resolution and within ten days the miliary infiltration had completely resolved. Achlorhydria gastrica was discovered. The author assumes that this patient had had a simple achlorhydric anemia for some months and that a streptococcal infection had rendered her a victim of streptococcal septicemia with a pul-

monary localization of a miliary appearance.
—*Streptococcal Miliary Infiltration of the Lungs*, P. Ellman, Brit. M. J., January 26, 1946, 1: 127.—(D. H. Cohen)

Tomography in Pneumonia.—The radiological aspects of 13 cases of childhood pneumonia are discussed. The common feature of all X-ray pictures was the so-called pneumonic triangle in the right upper lobe, the apex pointing towards the hilum and the base towards the axilla. Tomographic studies revealed that the area of consolidation was present at all levels, demonstrating the involvement of the peripheral as well as of the central layers of the lung. The triangular outline was most sharply defined at the 7 and 9 cm. levels.—*M. Mouriquand & J. Savoye, Presse méd., October, 1946, 635.*—(V. Leites)

Pneumatocele in Pneumonia.—Pneumatocele (synonymous with emphysematous bulla or "benign cavity") is a frequent occurrence during the course of pneumonia in children. It is essentially a roentgenological diagnosis, the incidence depending on the frequency of roentgenograms taken during the disease. The phenomenon is brought about by a check valve action of an inflammatory mucosal swelling of the bronchus, thus creating obstructive emphysema. Lister demonstrated the positive pressure by manometric measurements in a six-month-old infant. The readings varied between plus 2 and plus 4 mm. of mercury on inspiration, and plus 4 and plus 10 mm. on expiration. Laurell produced emphysematous blebs and bullae which cast ring shadows in the roentgenogram by inflating excised calf lungs; microscopically they "were revealed to be belts of compression atelectasis of the alveoli contiguous with the border of the emphysematous air pocket." The differential diagnosis comprises: (1) acute pulmonary abscess; (2) aputrid pulmonary necrosis due to infarction; (3) tuberculous cavity; (4) localized pneumothorax; (5) congenital pulmonary cyst; (6) regional obstructive emphysema in the form of pneumatocele. Pneumatocelles may appear in minimal or in extensive pneu-

monia at any stage, they usually produce no symptoms and regress spontaneously during a few days to several months. Complications are rare, but there may be rupture with spontaneous pneumothorax. One case was reported in which a large pneumatocele caused dyspnea, cyanosis and cough. The authors tabulate 7 cases of their own which occurred within eleven months, among 50 cases (14 per cent) of pneumonia in children; one of the most severe cases is described in detail. The lesion always occurred in the area involved by the pneumonia. The pneumonia varied considerably in severity and duration (from seven to forty days). The pneumatocele appeared from the second to the twenty-fifth day after onset of the pneumonia. More than one pneumatocele developed in 3 cases. The size varied from 1 to 3 cm. in diameter. Fluid ocele lasted from four to forty-one days after discovery. In uncomplicated pneumatoceles no treatment is indicated.—*Pneumatocele During the Course of Pneumonia in Children*, J. R. Almklov & A. Hatoff, Am. J. Dis. Child., November, 1946, 72: 521.—(O. Pinner)

Loeffler's Syndrome.—Creeping eruption (cutaneous helminthiasis) is characterized by serpiginous elevated reddish tunnels or burrows, usually at the exposed surfaces of the skin, it is caused by nematodes (filariform larvae of *Ancylostoma braziliense*). Of 52 cases of creeping eruption who were studied for fourteen days or longer, 26 developed Loeffler's syndrome. With the exception of mild cough in 9 cases, there were no symptoms. There was eosinophilia of blood and sputum. Roentgen examination revealed patchy lung infiltrations. Neither nematodes nor ova were found in 204 stool examinations. No nematodal larvae were found in 381 sputum examinations. The sedimentation rate was normal in most cases. The pulmonary lesions are believed to be due to an antigenic response to the larvae or their exotoxin. The treatment of the cutaneous lesions consists in the application of ethyl chloride. The pulmonary lesions subsided with the treatment of the skin

lesions.—*Loeffler's Syndrome Associated with Creeping Eruption (Cutaneous Helminthiasis): Report of Twenty-Six Cases, D. O. Wright & E. M. Gold, Arch. Int. Med., September, 1946, 78: 503.*—(G. C. Leiner)

Loeffler's Syndrome.—A 26-year-old woman whose routine chest X-ray film showed a small oval ill defined opacity in the right mid-lung field and whose differential count showed up to 67 per cent eosinophils in the blood was found to have many ova of *Trichiuris trichiura* in the stool. The X-ray film appeared to clear spontaneously and the eosinophilia gradually decreased and disappeared after treatment for the infestation. A 47-year-old soldier admitted to the hospital with symptoms of cough, fever, weight loss and generalized chest pains, with changing infiltration on successive X-ray examinations, and a blood eosinophilia of from 12 to 25 per cent was treated with arsenicals, antimony and emetine on suspicion of schistosomiasis or other undetermined infestation, and had numerous relapses before he finally cleared after nearly two years of treatment. The first case seems to fit the original description by Loeffler, the other may be related but is much more severe and protracted, and differs in other manifestations.—*Pulmonary Infiltrations Associated with Blood Eosinophilia, Capt. I. Grayce, Clin. Proc., (J. Cape Town Post-graduate Med. A.), July, 1946, 5: 195.*—(E. Bogen)

Suppurative Pneumonitis.—The criteria for inclusion in this series of 27 cases of spreading suppurative pneumonitis were pneumonitic changes associated with cavity formation and a productive cough with purulent sputum. In the early stages, roentgenograms showed a homogeneous opacity which was not completely segmental. Later a translucent patch appeared in the opaque area indicating softening and excavation. In 9 cases, the earliest lesions were located in areas where acute putrid abscesses rarely are found. Subsequently, there was direct extension of the consolidation to the immediately adjoining areas. This was associated with some degree of reso-

lution in the original area; then, the newly involved area underwent cavitation. In most cases, the whole lung was involved at some time or other. Transient cavities generally appeared as translucent areas with smooth walls. Persistent cavities had irregular walls with serpigenous outlines. In these, the tributary bronchi usually were patent. After subsidence of the acute process, there was considerable residual damage in the form of fibrosis and bronchiectasis. Cavities persisted in 11 cases. Twenty-five of the patients were middle-aged males. The clinical course was characterized by cough, copious expectoration of purulent sputum, chest pain, sweating and prostration. Physical signs were variable and at times indicated bronchopneumonia, consolidation or cavitation. In 23 cases, the sputum had a fetid odor at one time or other. No organisms of etiological significance were found. Remissions and relapses were characteristic of the clinical course. Pathological changes were ascertained by autopsy in 6 out of 10 fatal cases and in 3 pneumonectomy specimens. There were extensive adhesions, thickening of the septa, areas of emphysema, collapse and pneumonitis, multiple abscess cavities and enlargement of lymph nodes. There was nothing specific about the histological picture of the abscess cavities. These were often multiple, with bronchial communications. Different cavities in the same lung varied. The cavities often were epithelialized. Bronchiectasis was not a prominent feature. A sharp differentiation between putrid and non-putrid abscess is not valid. A new classification of pulmonary abscess is suggested. The prognosis is poor. There were 10 deaths. The average duration of hospitalization in the surviving cases was eight and one-half months. Of these, 8 improved, but had residual symptoms. There were only 5 cures with conservative therapy; the other 4 cures were accomplished by pneumonectomy. Sulfonamide drugs were disappointing. Penicillin gave better results, especially in the acute stages. Drainage operations and collapse measures were completely unsuccessful. The indications for re-

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section (usually pneumonectomy) were (1) as a life-saving measure during the acute stage and (2) the advanced chronic stage, characterized by cavitation and bronchiectasis.—*Spreading Suppurative Pneumonitis*, T. H. Sellors, L. G. Blair, L. E. Houghton, J. C. Thompson & D. M. Pryce, *Thorax*, September, 1946, 1: 146.—(A. G. Cohen)

Intrabronchial Penicillin.—The paper is based on 63 cases of pulmonary abscess treated with endobronchial instillations of penicillin. A general review of bronchial divisions and pulmonary segments is given, illustrated by X-ray films of the bronchial catheter in the various positions. The majority of abscesses (40 per cent) were localized in the dorsal superior segment, 13 per cent in the apical segment, 15 per cent in the anterior segment of the right middle lobe, 13 per cent in the apex of the lower lobes. It was in most cases possible to direct the catheter into the bronchial division of the involved pulmonary segment and to instill the penicillin at the proximity of the abscess or even into the abscess itself. Good clinical and roentgenological results were obtained in 40 per cent of cases; 32 per cent were greatly improved.—*Aspects radiologiques des cathétérismes zonaires du poumon au cours de la pénicillinothérapie endo-bronchique, des abcès pulmonaires*, C. Mattei, M. Tristan & A. Barbe, *Presse méd.*, October, 1946, 638.—(V. Leites)

Monaldi Drainage of Lung Abscess.—A large pulmonary abscess situated in the right lower lung field was treated by the Monaldi method of aspiration. The temperature became normal after five days. Fifty to 75 cc. of pus were evacuated daily, using negative pressures of 75 to 100 cm. water. After five weeks the abscess was not visible on X-ray films. Lipiodol studies showed that the draining bronchus had remained open. The tube was withdrawn after fifty days. The external opening closed up in less than one week. There was a marked improvement of the general condition. The patient was kept for further two months under observation with-

out showing signs of relapse.—*Un cas d'abcès du poumon traité par drainage et aspiration continue*, A. Lemanissier & G. Forestier, *Rev. de la tuberc.*, 1944-45, 9: 500.—(V. Leites)

Respiratory Diseases.—All patients with acute disease of the respiratory tract of any type admitted to a large station hospital were studied. Hemolytic streptococci of group A were isolated from the throats or the nasopharynges of 342 men. Of these, 300 (87.7 per cent) showed antibody response. In 78.8 per cent there was severe or extremely severe sore throat. Headache was present in 77.8 per cent, general aching in 59.4 per cent, chills in 63 per cent, cough in 42.3 per cent, hoarseness in one per cent. Tonsillar and pharyngeal exudate in small amounts was present in 18.3 per cent, in large amounts in 44 per cent. No exudate was found in 37.7 per cent of the patients with proved hemolytic streptococcus infection. Edema of the pharyngeal tissues was seen in 85.7 per cent. Redness of the palate, anterior pillars and other pharyngeal tissues was absent in only 3 per cent. Tenderness of the anterior cervical lymph nodes was found in 80.9 per cent, fever in nearly all patients. The total leucocyte count was increased in 76.9 per cent, the erythrocyte sedimentation rate was accelerated in 91.3 per cent. The tonsils had been removed in 33 per cent of the men with streptococcal infections and in 34.4 per cent of the men with nonstreptococcal infections. Exudate and edema were more extensive and more frequent in the presence of tonsils than in their absence. A scarlatiniform rash was observed in 27 patients. Febrile hemolytic streptococcus infection may be present in persons with only slight abnormalities of the throat. In 10 per cent of the patients with proved streptococcal infection there was no or only minimal swelling of the throat. No hemolytic streptococci could be isolated from the nasopharynges or throats of 871 patients with symptoms and signs of disease of the respiratory tract. Of these, 66.3 per cent showed no or minimal sore throat, 83.3 per cent had cough, 13.1 per cent developed hoarseness. No exudate was

present in the throat of 95 per cent. In 15 patients there were large amounts of tonsillar exudate. Edema of the nasopharyngeal tissues was present in 10.9 per cent, redness in 23.8 per cent, adenitis in 13.6 per cent. Ten per cent of the patients with definite nonstreptococcal diseases presented signs suggesting infection by hemolytic streptococci. Group A hemolytic streptococci were present in the throats of from 5 to 20 per cent of the healthy camp population. No method is available for differentiating the nonstreptococcal infection of the respiratory tract which occurs in a hemolytic streptococcus carrier. Ten per cent of nonstreptococcal infections resemble clinically those caused by streptococci. Ten to 20 per cent of them occur in hemolytic streptococci carriers. Therefore, one to 2 per cent of nonstreptococcal infections will be believed erroneously to be streptococcal infections.—*Hemolytic Streptococcal and Nonstreptococcal Diseases of the Respiratory Tract: A Comparative Clinical Study*, L. A. Rantz, P. J. Boisvert & W. W. Spink, *Arch. Int. Med.*, October, 1946, 78: 869.—(G. C. Leiner)

Virus Infections.—Virus infections of the respiratory tract account for 32 per cent of the home visits and for 15 per cent of the office visits of the general practitioners. They are rarely a direct cause of death but they precede or incite many other serious infections. The causative agents are harbored in patients and in asymptomatic carriers who serve as migratory sources of infection. Epidemics are most common and most wide-spread in winter but they occur in all seasons and in all climates. Immunity is believed not to last beyond several weeks or months after an attack, except in influenza. Local resistance appears to be largely dependent on an intact mucous membrane with its normal coating of mucus kept in motion by gravity and ciliary and muscular activity. In spite of many similarities the following entities can be distinguished on the basis of clinical, epidemiological and etiological factors: the common cold, pharyngitis and tonsillitis, grip, febrile catarrh, viroid, influenza A and B. The common cold attacks

the nasal lining. Pharyngitis and tonsillitis cause sore throat. Constitutional symptoms predominate in grip and febrile catarrh. Viroid includes the nonpneumonic forms and viral pneumonias. It is characterized by dry inflamed membranes with cough. Influenza is clinically indistinguishable from other viral infections but its etiological diagnosis is essential for the efficient use of the anti-influenza vaccine. In recent years wide-spread epidemic diseases have been observed in which symptoms of gastro-intestinal disorder predominate over those arising from the respiratory tract. This group is called viral dysentery. Preventive measures such as cold vaccines, diet, tonsillectomy are of no value. Except for influenza vaccine there is no specific vaccine. Obstructive adenoids may bear a relationship to frequent colds and should be corrected surgically. Nothing can be done to shorten attacks of viral infections of the respiratory tract. A critical appraisal of many preventive and therapeutic measures in common use shows them to be of no avail. Rational therapy consists of rest and analgesics if necessary. Vasoconstrictive drugs should be used as seldom as possible. Inhalation of steam, lozenges or codein in small doses may be helpful in combating a cough caused by irritation or dryness of the upper respiratory passages.—*Viral Infections of Respiratory Tract: Their Treatment and Prevention*, H. A. Reiman, J. A. M. A., November 2, 1946, 132: 487.—(H. Abeles)

Miliary Virus Pneumonia.—The recognition of this form of virus pneumonia is of importance because of the roentgenological similarity to miliary tuberculosis, and the marked difference in prognosis. Seven cases of miliary virus pneumonia are described, of which 4 were fatal. After prodromal symptoms of several days to weeks, the patients became acutely and seriously ill with fever and severe cyanosis and dyspnea. Recovery ensued slowly over a period of from ten days to six weeks, and death was observed from fourteen to forty-five days. The immediate cause of death was slowly developing circulatory failure. Physi-

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cal examination, in addition to the obvious cyanosis and dyspnea, revealed rather tympanitic lungs with many fine and medium moist râles, similar to those heard in pulmonary edema. The laboratory studies showed only rarely elevation of white cell counts, but in all cases a marked increase in the neutrophils and a shift to the left, with toxic granulations, was observed. X-ray films showed typical miliary foci throughout both lungs, which, in contrast to those of miliary tuberculosis, were less dense in the upper lobes. The cold agglutinin titer was markedly elevated in 3 out of 4 cases in which this test was done. Postmortem examination showed a remarkably uniform picture. There were small bronchopneumonic foci scattered throughout. Some alveoli were filled with cellular exudate, but the majority showed invasion by new connective tissue with fibroblastic proliferation and many new capillary loops. The bronchioli were almost invariably included in this proliferative process and a true obliterating fibrous bronchiolitis was thus observed. The interalveolar septa were infiltrated with cells and widened. Hemorrhagic tracheitis or bronchitis was notably absent. Treatment is generally supportive, consisting of oxygen and penicillin and sulfa therapy. Convalescent blood should be given as it seems to have been of distinct value in the one case in which it was procured. Care should be exercised in determining the proper blood group because of the possible error involved in a case with a high cold agglutinin titer.—*Über miliare Pneumonie von eigenartig schwerem Verlauf*, W. Löffler & S. Moeschlin, *Schweiz. med. Wchnschr.*, September 7, 1946, 76: 815.—(H. Marcus)

Chemical Pneumonitis.—Seventeen cases of a peculiar delayed pneumonitis were observed; all worked in a fluorescent lamp manufacturing concern where beryllium compounds are used. Symptoms developed only after long periods of exposure; in some patients, symptoms appeared as long as three years after discontinuing work. A great variety of symptoms were seen but chiefly the patients complained of anorexia, weight loss, dyspnea on exertion and cough. Blood counts and sedimentation rates showed only slight deviations from normal. Tubercle bacilli were never recovered from any of these patients. Fever was low grade except for terminal elevation. In the early stages, chest films revealed a fine diffuse sandpaper appearance. Subsequently, a diffuse reticular pattern appeared on the granular background to be followed, in the progressive cases, by distinct scattered nodules. Sulfonamide and penicillin therapy was not effective. Six patients died after illnesses of months and years. Six patients showed gradual improvement, one is completely well and 4 are still ill and disabled. Postmortem examination of one patient revealed diffuse granulomatous infiltration and fibrosis of the lungs and hilar lymph nodes. The cellular infiltrations were composed of lymphocytes, plasma cells, macrophages, epithelioid cells and giant cells; these cells were diffusely spread without any particular arrangement. Similar granulomatous changes were present in the liver. The spleen was enlarged and fibrotic. The right side of the heart was markedly dilated and hypertrophied. The etiology of this condition is not yet clear. Histologically, there are certain similarities to Boeck's sarcoidosis. The common occupational environment is suggestive. The authors believe that exposure to beryllium compounds is of etiological significance.—*Delayed Chemical Pneumonitis Occurring in Workers Exposed to Beryllium Compounds*, Harriet L. Hardy & I. R. Tabershaw, *J. Indust. Hyg. & Toxicol.*, September, 1946, 28: 197.—(H. R. Nayer)

Cystic Disease of Lung.—Included in this group are a number of conditions variously called pulmonary cysts, bronchogenic cysts, congenital cystic disease of the lungs and pneumatoceles. Here also are the cyst-like cavities sometimes produced by bronchiectasis. The following working classification is offered:

- I. True developmental or so-called congenital cysts of the lungs, including some of the bronchogenic or broncho-alveolar cysts.

II. Acquired cysts:

- a. "Cystic" bronchiectasis.
- b. Other pulmonary cysts.
 - (1) Pneumatoceles.
 - (2) Abscess cysts.
 - (3) All other types; these arise from infection, penetrating wounds, noxious gasses, hemorrhagic effusions, etc.
 - (4) Emphysematous blebs.
 - (5) Emphysematous bullae.

The developmental cysts are usually large, from 4 cm. up to huge dimensions. The cyst occupies an eccentric position in relation to its communicating bronchi which are normal, though often small and imperfect. The essential histological picture is one of uniformity in the lining membrane which maintains the regular character of the bronchial epithelium which is in contrast to the disorderly arrangement and erratic grouping of the supporting structures of the wall. In cystic bronchiectasis the cysts are smaller (2 to 4 cm.), located usually in basilar lobes; the bronchi enter cysts directly and always show dilatation and thickening of wall. The pneumatocele has no epithelial lining and, therefore, may subside spontaneously. In clinical practice it is difficult to be certain which cysts are of the developmental type and which are acquired. The large cysts found in accessory or aberrant pulmonary tissue are probably congenital. The picture at operation may be very simple and uncomplicated or it may be very bizarre in the presence of hemorrhage and infection. Hemoptysis or even severe pulmonary hemorrhage is not uncommon and was found in 73 per cent of this series. These cases because of their cough, sputum and hemoptysis are frequently diagnosed tuberculosis. Bronchoscopy is of value before surgery to rule out the possibility of other bronchial lesions and to aid in the localization of the cyst. A large infected cyst very closely resembles a loculated empyema. The ideal treatment is complete operative removal of the cystic portion of the lung.

Drainage of the cysts and other supplementary operations are usually not satisfactory.—*Cystic Disease of the Lungs and Its Relationship to Bronchiectatic Cavities*, J. A. Dickson, O. T. Clagett & J. R. McDonald, *J. Thoracic Surg.*, June, 1946, 15: 196.—(W. M. G. Jones)

Pulmonary Cyst.—Case report of a 4-year-old child who developed fever following measles. X-ray films revealed large cystic formations in the right lower lung field. Tuberculin test and gastric lavage were negative. Infected congenital cysts or giant emphysematous bullae were considered as a differential diagnosis. A right spontaneous pneumothorax and empyema developed one week later and were treated with tube drainage. Complete reexpansion ensued. X-ray films a few months later showed complete disappearance of all abnormal shadows in the right lung field.—*Images pulmonaires pseudo-cystiques, pneumothorax spontané, guérison*, F. Toury & J. Vicaire, *Rev. de la tuberc.*, 1946, 10: 48.—(V. Leites)

Pulmonary Cysts.—Two types of cysts are commonly recognized: (1) bronchial cysts, whose inner lining reveals bronchial epithelium and whose wall contains smooth muscle, glands and cartilage; (2) giant emphysematous bullae, the development of which is due to progressive atrophy of alveolar walls. Giant bullae are believed to be acquired in the course of life due to inflammatory or trophic changes of the alveolar walls. They appear in conditions associated with pulmonary sclerosis, (tuberculosis, silicosis), generalized emphysema or stenosis of the stem bronchi. It is commonly thought that bronchial cysts are of congenital origin. The authors believe that this concept is not sufficiently confirmed by facts. In their opinion no histological proof exists, which could ascertain the congenital or acquired origin of a cyst. The origin has to be evaluated with the help of all data in each single case. It is emphasised that in numer-

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ous specimens of congenital cysts, the characteristic histological features, as described above, were absent. On the other hand, the fibrous wall of an acquired cyst with associated inflammatory changes showed bronchial structures (muscular, adenomatous and cartilaginous tissue), corresponding to dissociated elements from a neighboring bronchus involved in the process of inflammation and fibrosis, or to muscular and pseudoadenomatous new-formations frequently seen in chronic inflammations of the lung. Thus, acquired bronchial cysts (or cystic bronchiectasis) may be due to an obstruction or a peribronchial inflammation of the stem bronchus. Chronic pulmonary abscesses with secondary epithelialization may be indistinguishable clinically and roentgenologically from bronchial cysts. In these cases the differential diagnosis between abscess cavity, secondary suppuration in a congenital cyst and giant cystic bronchiectasis can only be made by detailed histological examination of the cavity wall at different points.—*A propos de l'origine acquise de certains kystes pulmonaires bronchiques de l'adulte, Santy, Berard, Galy & J. Dumarest, Le Poumon, January-February, 1946, 2: 5.*—(V. Leites)

Experimental

Asbestosis.—Experiments were carried out on four groups of rabbits: (1) intratracheal introduction of 100 mg. of Rhodesian asbestos fibers 15 μ long, at monthly intervals; (2) same, but with the addition of 2 mg. of metallic aluminium to each dose; (3) as in group 1, but with fibers only 2.5 μ long; and (4) same, but with fibers only 2.5 μ long. In all groups, the lungs showed foreign body reactions. In the long-fiber experiments, there was a nodular reticulosis comparable to the silicotic nodule. In the short-fiber experiments, there was diffuse interstitial reticulosis. The addition of aluminium did not influence the effect of the asbestos particles.—*The Effect of Asbestos and of Asbestos and Aluminium on the Lungs of Rabbits, E. J. King, J. W. Clegg & V. M.*

Rac, Thorax, September, 1946, 1: 188.—(A. G. Cohen)

Thoracic Wounds.—Broad principles of therapy are presented, based on the experience of an auxiliary surgical group in the management of about two thousand thoracic casualties in the Mediterranean theater. This group worked in a field hospital; the bulk of thoracic cases consisted of open pneumothoraces, thoraco-abdominal wounds, wounds of the heart, esophagus, trachea or large bronchi, wounds with severe continuing hemorrhage and wounds with pressure pneumothorax. The group also participated in the work of base section hospitals. The early treatment of thoracic wounds, except for external débridement, is conservative. Thoracotomies within the first forty-eight hours for removing metallic foreign bodies, evacuation of a hemothorax or the suture of a lacerated wound yield an increase in the empyema rate, poorly expanded lungs and a higher mortality, when compared with similar operations done at a later time. Emergency service comprises: (1) replacement of blood loss by transfusion; (2) relief of pain and restlessness, but morphine must be used with great caution (for thoracic wall pain, intercostal nerve block was found most effective); (3) cardiorespiratory stabilization by a combination of thoracocentesis if more than 500 cc. of blood are present, autotransfusion, intercostal insertion of a needle attached to a water-trap bottle if there is pressure pneumothorax, oxygen, occasionally continuous Wangensteen suction, establishment of adequate airways; (4) prevention of infection. Traumatic wet lung, a syndrome characterized by increased pulmonary secretion and faulty bronchial drainage, may be the sole cause of death. This is associated with a constant, inefficient cough, dyspnea, at times pulmonary edema, asthmatoïd conditions or hemoptysis, and lobar atelectasis during the later phase. The treatment consists of control of the thoracic wall pain by nerve block, frequent change of the patient's position, carbon dioxide, aspiration

of bronchiopulmonary secretions, if necessary by bronchoscopy. For pulmonary edema atropine is given intravenously; oxygen and venesection may be indicated. Chemotherapy should be but an adjunct to surgery. In thoracic wounds crystalline sulfanilamide has been used routinely. Sulfadiazine has been replaced by penicillin more recently. The important rôle of a competent anesthetist is stressed. Adequate equipment has been available for endotracheal technique and positive pressure. Most frequently oxygen-ether vapor has been employed. Bronchoscopic aspiration has become almost a routine procedure at the end of operation. Sucking wounds are treated with simple occlusion on the battlefield. Thoraco-abdominal wounds are frequent, they have a fatality of about 35 per cent. Separate thoracotomy and laparotomy should be avoided if possible. In right-sided injuries laparotomy is almost always necessary. Frequently the "traumatic thoracotomy," resulting from débridement of a sucking wound, is sufficient to determine that only the liver and/or kidney has been injured, and to do a transdiaphragmatic nephrectomy, if indicated. On the left side a ninth intercostal incision will give ample exposure for splenectomy and the examination of some of the intraabdominal organs. Diaphragmatic repair should be meticulous. Wounds of trachea and extrapulmonary bronchi are rare. There is an extreme pressure pneumothorax and rapid complete collapse of the lung. Extensive subcutaneous and mediastinal emphysema has been noted. Early closing of the defect is necessary. This may not be possible with large defects of the main bronchi; lobectomy or even pneumonectomy may be necessary. Pressure pneumothorax is no indication for immediate thoracotomy, except when caused by wounds of the trachea and bronchi. Usually the pulmonary defect will close on insertion of an intercostal water-seal drain. The insertion of a catheter in an upper anterior interspace is recommended. Early hemothorax is not emptied during the first two or three days; moderate pulmonary compression may aid

in controlling parenchymal oozing. Thereafter, at least once a day, the pleural cavity is emptied by thoracocentesis as rapidly and completely as possible. The results are excellent. Air replacement is not used in forward hospitals. In most cases of pure traumatic pneumothorax with not more than 25 to 30 per cent of lung compression, spontaneous reëxpansion will be evident after ten to fourteen days. Organizing hemothorax is caused by the organization of blood frequently encountered in the pleural cavity. A "peel" or "rind" develops, continuous over visceral and parietal pleura. Extensive processes may lead to chronic pulmonary crippling and even the formation of calcium plaques. The infection rate, including infections following thoracotomies, has been about 20 per cent. In small hemothoracic empyemata the treatment has been airtight rib resection drainage, followed in seven to ten days by open drainage. Total pulmonary decortication, in selected cases, has resulted in a great decrease in the convalescing time and a reduction in the possibility of pulmonary impairment. In 75 per cent of all infected cases the lung expanded promptly without a residual empyema. In the remainder, the empyema has been basal and adequate drainage has been easily maintained. Operation for fractured ribs was indicated when there was extensive comminution, continued bleeding, continued trauma to the lung or bronchopleural fistula. Delayed operation may be indicated if persisting thoracic wall pain is associated with ununited fractures or extensive scar tissue and callous formation. Strapping has been discarded; instead, nerve-block was employed, giving freedom from pain for twenty-four hours and, therefore, greatly facilitating transportation. Wide pulmonary resection in forward hospital is indicated only when there is irreparable damage to a major bronchus or partial traumatic amputation of a lobe or damage to the main pulmonary veins which necessitates their complete ligation. Two total pneumonectomies were performed by this group; the mortality is high, as is that from

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lobectomies in forward hospitals.—*Management of Thoracic Wounds in an Overseas Theater*, P. C. Samson & T. H. Burford, *Bull. U. S. Army Med. Dept.*, December, 1946, 6: 709.—(O. Pinner)

Air Blast Injuries.—Air blast is the complex of three types of waves set in motion by the detonation of an explosion: (1) a positive pressure wave, rising to its maximum intensity within 0.0001 to 0.002 seconds, with an initial speed of two or three times the velocity of sound; (2) the windage phenomenon; (3) a negative pressure wave. Only the first two positive waves are of importance in producing blast injuries. The forces exerted by the waves decrease proportionately to the square of the distance from the centre of explosion. But if an obstruction of sufficient size is placed in their path, they are reflected and their pressures may be doubled. This is extremely important with respect to explosions occurring in closed spaces, especially in rock caves where multiple reflection will be produced. A peak pressure of about five hundred pounds per square inch appears necessary to produce a casualty rate of 50 per cent among men. Sensitivity to blast decreases with increased weight of the test subject. Diminution of efficiency was found in personnel exposed to pressures as low as two and one-half pounds per square inch, but the evaluation of efficiency is too vague to be of value. Although blast-wave-pressure tables give some clues as to the size of charge and bomb necessary to incapacitate personnel in a given area, blast waves may exhibit some erratic behavior, especially with personnel in caves. They are likely to be exposed to pressures much lower than they would experience at equal distances in the open as long as the detonation occurs outside the enclosure. With the detonation inside, the peak pressure may not only be higher but its duration longer. Regardless of the positions occupied by the personnel the effects of blasts are the same, but one of the several types of effects may predominate. The main categories of these effects are: (1) primary blast effects, due to the blast wave itself, to flames from the explosion or to gases given off by the explosive; (2) secondary blast effects, resulting from splinters or from personnel propelled by the bomb; (3) tertiary blast effects, produced by flying missiles or rock or collapsing masonry; (4) quaternary blast effects, including such factors as drowning, asphyxiation, burning. Lesions similar to those produced by blast may result from other reasons. Fatal injuries of the pure blast type are not frequent and probably occur only in the immediate vicinity of the explosion. The characteristic syndrome of air blast shows marked variation in the intensity of individual symptoms. There is a direct relation between the degree of restlessness of the victims and the severity of the blast. Some degree of shock is invariably present. Cyanosis, dyspnea and orthopnea are frequent and indicate lung injury. There may be enough, chest pain and sometimes hemoptysis. Physical examination of the chest at first reveals little; later on patchy consolidation, pleural effusion or pneumonia may become evident. There is almost always some injury to the ear. Pathologically, the most striking and consistent findings are in the lungs. There are hemorrhagic areas associated with rib lines and extending into the lung tissue. The anterior and lateral lung borders are most vulnerable. Emphysema and atelectasis may be associated with hemorrhage. The upper respiratory passages are frequently filled with blood. Laceration of lung tissue may occur. Microscopically, the areas of hemorrhage show extravasation of blood into alveoli and bronchi. Hemorrhage into any of the body tissues and rupture of organs may be seen. The rupture of lung tissue is due to body impact or the compressive force of the wave driving the thoracic cage against the lungs, with compression of the abdomen forcing the diaphragm upward and increasing the impact. Therefore, the main value of the atmospheric blast as a weapon lies in the secondary condition arising from its action. Earlier experiments were made with smaller charges. From one of the

experiments, involving the use of 1,750 lb. of TNT, it was concluded that "air blast is a minor and infrequent hazard." In the experiment reported in this paper, 9,600 lb. of TNT were detonated. Eight adult goats were placed in six excavations made in a hillside, each designed for one or two persons; 7 additional animals were staked in the open. Each linear charge, 320 ft. in length, contained 4,800 lb. of explosive encased between thin corrugated plates. Both were detonated within a minute. Thereafter, each animal was examined for external injuries and abnormalities and then killed by intracardiac injection of magnesium sulfate. Trachea, lungs, heart, liver, kidneys and intestinal tract were inspected. Microscopic studies of the lung tissue were made but are not reported. The effects are tabulated, and a survey of the autopsy findings is given. Of the 7 goats kept in the open, one was dead and showed severe injuries to the lung; it had been staked between the two charges and exposed to a possible augmentation of the blast by reflection from adjacent hillsides. The blast effect on 3 of these animals was considered slight, 3 others escaped. Of the 8 goats kept in emplacements, one was buried by a cave-in and found dead the next day, apparently from asphyxia. It suffered moderate injury to the lung, possibly as a result of the cave-in and not of the blast. The findings in 2 of the surviving 7 animals are listed as moderate, in the remainder as slight; pulmonary lesions were not common. Only one animal showed damage to the liver. A goat placed in the immediate proximity of the charge was not injured. Such vagaries of air blast effects have been noted under actual combat conditions. However, goats and other small animals are not so resistant to blast as man is. Therefore, similar damage might not have occurred if human subjects had been used in these experiments. The importance of air blast in neutralizing personnel has been highly overestimated.—*Experimental Study of Air Blast Injuries*, S. M. Horvath & W. B. Shelley, *Bull. U. S.*

Army Med. Dept., December, 1946, 6: 761.—(O. Pinner)

Spontaneous Pneumothorax.—A case of spontaneous pneumothorax is reported, which occurred in a 5-day-old white girl, delivered by cesarean section. At delivery the infant was cyanotic and cried weakly but respiration and physical findings were normal. Resuscitation consisted of bulb suction and eutaneous stimulation. On the fifth day her temperature was 103.6° F.; the infant was cyanotic, dehydrated, lethargic and flaccid and had a mild convulsion. The white count was 17,000 with 54 per cent polymorphonuclear leucocytes and 46 per cent lymphocytes. A chest roentgenogram revealed a right pneumothorax; the same was found the next day, while the temperature was normal and an examination of the chest revealed nothing remarkable. Another roentgenogram taken four days later showed complete absorption of the pneumothorax air, and on three occasions during the following year roentgenograms of the chest were normal. Spontaneous pneumothorax in the newborn infant is relatively rare. The diagnosis can be made only by roentgenography. Treatment should be conservative, aspiration should be reserved for the more severe forms. Trauma during delivery probably plays a major rôle.—*Spontaneous Pneumothorax in the Newborn*, E. P. Scott & C. C. Rotondo, *Am. J. Dis. Child., August, 1946, 72: 207.—(O. Pinner)*

Spontaneous Pneumothorax.—At a large military post, 41 cases were seen in four years. The onset was sudden in all but one case. Chest pain was present in all. It was frequently found over the affected lung and sometimes radiated to the shoulder, neck, lower back and abdomen. Dyspnea was present in all. There was cough in 7 cases, cyanosis in 3, mild collapse in 3 and fever in 2 (with active tuberculosis). The onset occurred while the soldier was at rest in 23 cases, during mild physical effort in 10 and during vigorous physical exertion in 5. The most constant physical findings were dimin-

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ished or absent breath sounds. There was almost equal involvement of both sides. Tuberculin tests performed in 12 cases showed a positive reaction in 6. X-ray films of the chest showed active, far advanced pulmonary tuberculosis in 2 cases, inactive minimal disease in 3 and calcified primary disease in 4. Films in the other cases were normal. The degree of collapse was considered mild in 51 per cent, moderate in 26 per cent and extensive in 23 per cent. In practically all cases, the lung re-expanded on bed-rest and symptomatic medication; aspiration of air was necessary in 3 cases, 2 of which were those with active tuberculosis.—*Non-traumatic Spontaneous Pneumothorax among Military Personnel*, S. Cohen & J. M. Kinsman, *New England J. Med.*, September 26, 1946, 235: 461.—(A. G. Cohen)

Spontaneous Pneumothorax and Aerial Ascent.—In view of the present interest in aerial ascent, 2 cases of spontaneous pneumothorax are reported along with data concerning the incidence of spontaneous pneumothorax occurring during altitude chamber flights. The records of 86,916 man-hour flights in the altitude chamber were surveyed, the flights consisting of approximately ninety minutes' duration with a simulated altitude of 30,000 feet. Only one man developed a spontaneous pneumothorax and in one other case early descent was necessitated because of a pre-existing partial pneumothorax. Of 771 persons undergoing an "explosive" decompression flight no spontaneous pneumothorax occurred. These findings are in accord with most data published to date. Clark recently reported 2 cases of mediastinal emphysema. After surveying the literature and the records of the A. A. F. Regional Hospital at Lincoln, Nebraska, one may conclude that changes of altitude encountered in normal aerial flight have no appreciable bearing on the development of spontaneous pneumothorax in healthy persons. The second case reported is illustrative of the aggravation of a preëxisting pneumothorax upon ascent, the pleural cavity responding to Boyle's law. It has

been recommended that no person with a spontaneous pneumothorax ascend above 4,000 feet.—*Spontaneous Pneumothorax in Healthy Young Adults with Particular Reference to the Etiological Role of Aerial Ascent*, E. M. Heath, *Am. J. M. Sc.*, February, 1946, 211: 188.—(G. F. Mitchell)

Spontaneous Hemothorax.—A case report of spontaneous hemothorax is presented. The patient, a man aged 44, was in good health. One day, while riding in a tramcar, he was suddenly seized with pain of knife-like severity in the middle zone of the left side of the chest. Breathlessness developed simultaneously. He was weak and collapsed. The pain remained for several days, gradually decreasing in severity, but the dyspnea persisted. He was hospitalized eight days after the onset. He was orthopneic and the prone position increased the respiratory distress. There were signs of a massive left sided effusion with heart displaced to opposite side. A skiagram confirmed these findings—no air was noted. An exploratory thoracentesis revealed pure blood—65 per cent hemoglobin (Sahli). Further X-ray examination in two weeks showed a diminution in size of the effusion. In all, 1,500 cc. of blood were aspirated. Patient was discharged four weeks after admission. He was very comfortable. Physical examination eleven months later revealed no evidence of abnormality in the chest and a skiagram showed that the left lung field was now clear, except for slight pleural thickening in the costophrenic angle. In spontaneous hemopneumothorax the view is taken that following a spontaneous pneumothorax, the intrapleural pressure rises and any pleural adhesions which exist will become stretched and ultimately rupture, with blood added to the air in the pleural cavity.—*Spontaneous Haemothorax*, A. M. Crawford & J. Shafar, *Brit. M. J.*, January 19, 1946, 1: 88.—(D. H. Cohen)

Conflagration Injuries of Respiratory Tract.
—A total of 131 living victims of the Coconut

Grove fire were treated at the Boston City Hospital. Most of the persons who were dead on or soon after arrival appeared to have been asphyxiated. A few who appeared well suddenly coughed up frothy sputum and expired. There was close correlation between the extent of the surface burns and the severity of the respiratory complications. The general condition of the patients on admission varied with the extent of these two types of injury. There was evidence of smoke inhalation in almost all patients who had respiratory complications, especially in the worst cases. There was evidence of unconsciousness while still in the burning building in these cases; those with less severe injuries regained consciousness later. For purposes of this study, the cases were divided into five groups. The degree and frequency of symptoms and signs increased progressively from the groups of lesser to greater severity. The sputum generally was scant for the first one to two days. It contained soot and had the odor of smoke. Later it became mucopurulent and sometimes was blood-streaked. Fever was present in all except the mild cases. It was not related to antecedent respiratory infections. The most frequent symptoms were cough, soreness of the throat and hoarseness. Less frequent was pain beneath the sternum. Dyspnea, often associated with stridor or wheezing, was prominent in the more severe cases. Findings in the upper respiratory tract ranged from slight to extensive redness and edema of the nose, pharynx and larynx. Pulmonary signs varied greatly and included diminished aeration or consolidation of portions of the lungs and râles of various types. The roentgenographic changes are the subject of a separate report but, in general, they paralleled the physical signs. Tracheotomies were performed in 18 cases, of whom only 3 recovered. Most deaths occurred during the first twelve hours and after the fourth day. The chief damage was found to be a laryngo-tracheo-bronchitis. In severe cases, the inflammatory reaction was intense. It was accompanied by occlusion of various

parts of the respiratory tree by a pseudo-membrane of fibrin and by viscid and sanguineous exudate. Pulmonary damage was also present in such cases and consisted chiefly of congestion, edema and scattered areas of atelectasis, hemorrhage and infarction resulting from thromboses. Pneumonia was infrequent; when present, it was characterized by small necrotizing lesions. In treatment, simple nursing measures, such as gentle wiping of the mouth, frequent turning of the patient, etc. were important. Tracheotomy did not solve the problem of obstruction. Repeated aspirations of inspissated blood, mucus, fibrin and pseudomembranes *via* bronchoscope or catheter were required to maintain a free airway. Artificial respiration was life saving in one case. Oxygen administration did not help much, perhaps because the available apparatus was limited. Aminophyllin, ephedrine, epinephrine and atropine injections were not helpful in relieving dyspnea. Many different expectorants were used with varying benefit. Opiates were of value in relieving pain and barbiturates helped relieve restlessness. Inhalations of steam with added benzoin and also mechanical humidification of the air were considered of great value. Gentle local therapy of the oropharynx was important. The value of sulfonamide drugs was difficult to estimate: It was felt that they probably minimized the extent of pulmonary infection. Follow-up studies were carried out four, nine and twenty-six months after the fire. The most common residual symptom was persistent cough. This began in some patients a few months after discharge and was possibly due to bronchiectasis. The more severe cases generally had more residual symptoms.—*Clinical and Therapeutic Aspects of the Conflagration Injuries to the Respiratory Tract Sustained by Victims of The Cocoanut Grove Disaster*, M. Finland, C. S. Davidson & S. M. Lercenson, *Medicine*, September, 1946, 25: 215.—(A. G. Cohen)

Mikulicz's Disease and Typical Tuberculosis.—Case report of a 20-year-old male

patient presenting a chronic hypertrophy of both parotid glands with infiltration of the neighboring tissues, in association with an old bilateral cervical adenopathy. Spleen and liver were not enlarged. There was an episode of palpebral edema and lacrimation. Ophthalmological examination was negative. The lacrimal glands remained uninvolved. X-ray examination of the chest and skeleton was normal. The tuberculin test was highly positive. Histological examination of an enlarged cervical lymph node revealed a "tuberculoid" process characterized by reticulo-endothelial and epithelioid proliferation in the absence of caseation and giant-cell formation. The similarity of this histological picture with sarcoidosis was noted. No tubercle bacilli could be demonstrated on examination of the slides. Inoculation of the biopsy material into a guinea pig gave rise on the twenty-fifth day to a small nodule at the site of inoculation accompanied by regional adenopathy. Both lesions revealed a few tubercle bacilli on histological examination. The animal showed no visceral lesions. Biopsy of the parotid glands was not performed because of fear of fistula formation. The case was interpreted as a possible atypical tuberculosis, similar to sarcoidosis. It is admitted that the parotid involvement, similar to Mikulicz's disease, may have no etiological relation with the cervical adenopathy. — *Bacillose atypique: réticulo-endothéliose ganglionnaire cervicale de nature tuberculeuse au cours d'une maladie de Mikulicz, M. Bourgain & H. Laborit, Rev. de la tuberc., 1944-45, 9: 306.*—(V. Leites)

Sarcoidosis.—A colored male, aged 20, had a painless, nontender, spindle-shaped swelling at some joints of three fingers and a generalized, firm, shotty, nontender lymphadenopathy. Sputum concentrates were negative for tubercle bacilli. The serum proteins were 7.5 per cent with an albumin-globulin ratio of 2:1. The sedimentation rate varied from 7 to 13 mm., corrected. The tuberculin test was negative. The roentgenogram showed rarefaction, cystic changes,

widening of the phalangeal shafts and subperiosteal new bone formation in the involved fingers and the right hallux. Discrete bilateral enlargement of the hilar nodes and exaggerated lung markings were present. The roentgen diagnosis was sarcoidosis; this was confirmed by biopsy. During the thirty-eight days of hospitalization symptoms and signs concerning the fingers regressed but lymphadenopathy remained. Another patient, a white man, aged 26, complained of a gradually growing mass in the left supraclavicular region, a cough productive of mucoid sputum, anorexia, loss of weight. He had large, matted, nontender nodes in the left supraclavicular region and similar submental, infraclavicular, inguinal and femoral nodes. There were a few transient crepitant râles in the left apex. A hard, firm spleen was palpable. The sedimentation rate was 21 mm. Sputum concentrates were negative for acid-fast bacilli on smears and cultures. Roentgenograms revealed dense infiltrations in both lung fields, and large masses in both hilar regions. On biopsy, sarcoidosis was diagnosed. There was no change in the condition of this patient after three weeks of observation. The protean manifestations of sarcoidosis and its terminology are discussed. Inclusion bodies are sometimes found in the giant cells or in hyalinized tissue. The lesion progresses to fibrosis with hyalinization. Heavy coarse hyaline fibers encapsulate and eventually replace the granulomata. The lesion involves most frequently the lymph nodes, skin, bone marrow of the metacarpals, metatarsals and phalanges of hands and feet, lungs, spleen and liver; but any organ may be involved. The disease may end in apparent recovery, remain stationary or terminate in death from frank tuberculosis, myocardial involvement, pulmonary fibrosis, emphysema or *cor pulmonale*. The tuberculin test is negative in 70 per cent. Acid-fast bacilli are rarely found. There is often eosinophilia and monocytosis. The total serum proteins are often elevated because of an increase in gamma-globulin. The latter

may be increased at the expense of the albumin with the value of total protein being normal. One of the following clinical pictures presents itself: (1) *lupus pernio* or subcutaneous sarcoid with adenopathy, bone and pulmonary findings; (2) swelling of the fingers and toes with adenopathy and with or without pulmonary and skin changes; (3) uveoparotid fever; (4) Mikulicz's disease; (5) a cardiac picture; (6) any of the above findings with minimal symptoms. Roentgenologically, there is pulmonary or bone involvement or both. The lungs may show large bilateral shadows at the hila, with or without extension into the lung fields or a picture like miliary tuberculosis. These manifestations may remain unchanged for months and years, or gradually recede and disappear. The phalanges present medullar rarefactions and reticulation with irregular enlargement and distortion of the bones. The etiology is unknown. Most authors believe this is a form of noncaseating tuberculosis, the extreme representative of the productive reaction in tuberculosis. — *Sarcoidosis: Report of Two Cases*, M. Lev & C. L. Hinkle, *Bull. U. S. Army Med. Dept.*, November, 1946, 6: 617.— (O. Pinner)

Lung Cancer in Child.—The authors report a case of a primary lung cancer in a girl 9 years old. Onset was with pain in left thigh, worse on walking. There was no other systemic involvement and X-ray examination of the femur was normal. She was treated as osteomyelitis with sulphadiazine, and allowed home, to be under observation. One month later she was readmitted, pain persisting, and without other signs or symptoms. Skiagram now revealed circumscribed area of atrophy just below the epiphysial line of the greater trochanter. She was watched for a further six weeks at the end of which time the pain was fairly severe and continuous. X-ray examination revealed further bone destruction. All other laboratory and clinical work-up was essentially normal. Diagnosis of sub-acute osteomyelitis of the femur was now

made and an operation performed. Histological examination of tissue removed could not be identified with certainty, but the lesion appeared to be neoplastic. An X-ray film of chest at this time was considered negative. Patient received deep X-ray therapy for six weeks with evidence of "healing" of lesion. Eight months after original admission the patient was readmitted complaining of cough, headache and vomiting. She was emaciated and breathless. Clinical signs of a right-sided pleural effusion were found and aspiration revealed a small quantity of blood-stained fluid without evidence of neoplastic cells. Patient's condition gradually worsened and she died eight weeks after last admission. Necropsy revealed an enlarged mediastinum, displaced to the left. The right lung was almost entirely replaced by a large mass of necrotic malignant tissue arising from the upper main bronchus. The tumor had invaded the chest wall and the mediastinum. The left lung and the heart, apart from displacement, were normal. The abdominal viscera were all free from the neoplastic process. The upper end of the femur was replaced by yellowish necrotic tissue. Histological examination of the lung revealed a primary bronchial anaplastic carcinoma. The lesion in the femur was of similar histological structure. — *Primary Lung Cancer in Childhood*, A. Dick & H. Miller, *Brit. M. J.*, March 16, 1946, 1: 386.— (D. H. Cohen)

Surgery in Lung Cancer.—Out of 107 cases of lung carcinoma observed during the period from the end of 1943 until May, 1946, exploratory thoracotomy could be performed in only 21 cases. Asymptomatic development of many cases of early cancer accounts only partially for the late diagnosis; in a series of cases the physician who first treated the patient was responsible for the delay in the diagnosis. A practical and therapeutically significant classification of pulmonary carcinoma distinguishes: (a) carcinoma of the minor bronchi and (b) carcinoma of the major bronchi. In the former, exploratory

thoracotomy is the only reliable diagnostic procedure, while in the latter type the diagnosis can be ascertained by bronchoscopic examination. Exploratory thoracotomy is contraindicated by metastasis in other organs or in distant lymph nodes, by extension of the process to the chest wall, by the presence of vocal cord paralysis, Horner syndrome, diaphragmatic paralysis, pleural effusion or by poor general condition. Bronchoscopic findings indicating extension of the new growth in a main bronchus close to its origin from the trachea, or enlargement of the usually acute angle of the bifurcation of the trachea, or rigidity of the tracheobronchial tree represent also contraindications to exploratory thoracotomy. Out of 21 cases of thoracotomy there was one case of operative death due to acute emphysema. Pulmonary resection was possible in only 12 cases: pneumonectomy in 11 cases and left lower lobectomy in one case. Postoperative death occurred in 3 cases: in 2 cases death was due to bronchopleural fistula and putrid empyema; in one case bronchopneumonia developed and the patient died nine days after the operation. In one case of bronchopleural fistula continuous aspiration succeeded in closing the fistula and a three-stage thoracoplasty cured the empyema. Nine patients survived the operation for periods ranging from fifteen days to two years. In one case of survival signs of cerebral metastasis were noted one year and eight months after the operation.—*Nuestra experiencia en el tratamiento quirúrgico del cancer de pulmon, O. J. Cames, A. Cesanelli & F. E. Triccerri, Prensa méd. argent., August, 1946, 33: 1621.*—(L. Molnar)

Lung Tumor.—A report is given of a clinical-pathological conference of the Tumor Board at the Walter Reed General Hospital. Participating in the discussion were D. B. Effler, R. F. Bunch, V. H. Cornell, H. W. Jones, M. M. Greenfield and F. E. Hamilton. A case of lung tumor in a 52-year-old white warrant officer was presented. On a routine X-ray examination a lesion of the lower

lobe of the left lung was detected. Neither symptoms nor physical signs were present. The corrected sedimentation rate was 26. The coccidioidin tests were negative. The tuberculin test was positive. Smears, cultures and guinea pig inoculations of gastric washings were negative for tubercle bacilli. Roentgenologically, there was a well-defined but not sharply demarcated lesion in the mid-portion of the left lower lobe, 22 mm. in diameter. A moderate increase in the size of the shadow and in its density was observed within the last two weeks. Exploratory thoracotomy was recommended and patient was transferred to the Thoracic Surgery Section. The most likely diagnosis was tuberculoma of the lung but, with due consideration of the patient's apparent familial tendency to malignancy, a primary bronchogenic carcinoma or a solitary metastasis was not ruled out. A lobectomy was done. The pathological examination of the excised lobe showed a soft, fleshy nodule, 2.4 by 1.5 cm., with broadly serrated borders and a soft homogeneous centre, necrotic rather than caseous. No tumor was found in two small lymph nodes at the hilum, and no extension of the tumor beyond its edge was seen when the bronchi were opened. The microscopical picture is described in detail. The pathological diagnosis was adenocarcinoma, probably primary in lung, compatible with "alveolar carcinoma." Despite this classification the possibility of a metastatic lesion from the prostate, genito-urinary or biliary tract should be ruled out by further study. The cellular structure resembled so-called adenomatosis of the lung, a disease similar to the *jaagsiekte* of animals in which it is thought to be due to a transmissible virus. Based on hypothesis rather than statistics, the opinion was expressed that a bronchogenic tumor would be best treated by lobectomy. The purpose of the operation is the removal of as much tissue as possible between the tumor and the hilum, since the most common extension of the tumor is toward the mediastinum. Total pneumonectomy would not seem to increase the protection of the patient.

It was emphasized that the Surgical Service does not advocate lobectomy for all undiagnosed lesions detectable only by X-ray examination; but if location and X-ray appearance are compatible with a malignancy, radical excision beyond any reasonable area of metastatic extension is advocated.—*A Case of Lung Tumor, (not signed), Bull. U. S. Army Med. Dept., December, 1946, 6: 701.—(O. Pinner)*

Multiple Pulmonary Hemangiomas.—Because of the increasing interest in the accurate diagnosis of intrathoracic lesions and more successful thoracic surgery, a case of pulmonary hemangioma is reported, and the 7 cases previously reported in the literature reviewed. This rare condition, first reported by Rodes, consists of a knot of blood vessels connected by feeder vessels having both arterial and venous circulations; this acts as a shunt resulting in anoxemia. The patient reported was a young man, apparently well except for a polycythemia and the signs and symptoms referable to it including cyanosis, clubbing of the fingers, headache, ease of fatigue and slight dyspnea on exertion. There was also a peculiar murmur heard in the fourth interspace 5 cm. to the left of the mid-line and a small telangiectasis behind one ear. The symptoms were of three years' duration and there was no exposure to aniline dyes or heavy metals. The findings were not characteristic of a polycythemia vera. Fluoroscopy revealed no abnormality and electrocardiographic examination did not show signs of cardiac impairment due to pulmonary disease. Pulmonary hemangioma was suspected. An X-ray film revealed a fairly discrete opacity, 2 cm. in diameter, in the mid-portion of the right lung at the level of the eighth rib posteriorly and a poorly defined opacity in the seventh posterior interspace in the mid-portion of the left lung, interpreted at first as thrombotic vessels secondary to polycythemia. Laminography revealed dilated pulmonary vessels extending from the hilar region and the masses in the lung field showed an irregular worm-like

configuration continuous with the feeder vessels. All cases reported in the literature have been young adults having dyspnea, clubbing, cyanosis and polycythemia. In 3 of the 7 cases the hemangiomas were multiple. The prognosis is grave. Surgery is probably the method of choice.—*Multiple Pulmonary Hemangiomas, P. D. Makler & D. Zion, Am. J. M. Sc., March, 1946, 211: 261.—(G. F. Mitchell)*

Pleural Mesothelioma.—The case of a 35-year-old woman is presented in detail. *In vivo*, no definite diagnosis could be made, although primary endothelioma of the pleura was listed among the possibilities. The prominent symptom was pain in the chest which had been present for two years before the patient first consulted a physician and which was at first attributed to a fall suffered two years previously. Cough and dyspnea were also complained of. An X-ray film of the chest showed what appeared to be a serofibrinous pleurisy on one side. Fifteen months later bone metastases were found in a rib and in the pelvis. The patient was given palliative radiotherapy, but failed to respond and died approximately three years after the onset of symptoms. A diagnosis of primary pleural mesothelioma was made at autopsy. The clinical diagnosis of this rare tumor is quite difficult, since the symptoms (chest pain, cough, dyspnea) are not characteristic and the demonstration of tumor cells often fails. Pleural effusion, varying from thin, serous to grossly hemorrhagic fluid, is nearly always present; on thoracentesis one may feel the needle penetrating the tumor-thickened pleura. Metastases usually occur by direct extension to the adjacent structures. The histological origin of the tumor is a moot question. Pleural endothelium, endothelial cells of the subpleural lymphatics, aberrant nests of lung epithelium are favored by various authors; others believe that pleural cancer is always secondary to tumors originating elsewhere, for example, in the bronchi. The radiosensitivity of pleural mesothelioma is doubtful

at best. — *Primary Mesothelioma (Endothelioma) of the Pleura: Case Report, A. D. Piatt, Am. J. Roentgenol., February, 1946, 55: 178.*—(P. Lowy)

Hodgkin's Disease and Lymphosarcoma.—

It is pointed out that each type of body cell has a specific range of radiosensitivity. A classification in the order of sensitivity to irradiation is presented as follows: (1) lymphoid cells, (2) polymorphonuclears, leucocytes and eosinophils, (3) epithelial cells, (4) endothelial cells, (5) connective tissue cells. The more active the cell from a metabolic point of view, the more radio-sensitive. Sensitiveness of tumor cells corresponds closely to that of the cells from which the tumor is chiefly derived. This fact can be of great help in the differential diagnosis of intrathoracic tumors. Exposure to roentgen rays almost always differentiates between Hodgkin's or lymphosarcoma and an aneurysm of the aorta, between lymphoblastomata and bronchogenic carcinoma, teratoma or a desmoid tumor or tuberculous adenitis. Hodgkin's disease and lymphoblastoma often begin in the cervical nodes, nasopharynx or tonsil, but an equal percentage begin in retro-abdominal nodes. Usually mediastinal involvement is secondary to lymph node involvement elsewhere. Accurate differentiation of mediastinal Hodgkin's or lymphosarcoma from other tumors is not possible by X-ray alone. Upper mediastinal nodes are affected more frequently than those in the lower thorax. Usually the enlarging nodes project laterally, but only large or numerous nodes will project beyond the composite shadow. Yet smaller nodes may cause cough, shoulder pain, etc. All types of involvement respond well to radiation. Occasionally when involved nodes are high in the mediastinum, in addition to dyspnea with or without dysphagia there may occur a brassy cough, hoarseness due to recurrent laryngeal nerve involvement, puffiness and cyanosis of the neck and face and prominence of superficial veins. For some obscure reason, lymph nodes causing this picture do not

respond so effectively nor so rapidly to treatment as affected nodes lower in the mediastinum. Chest, shoulder, or upper extremity pain may be due to pressure on or actual infiltration of the brachial plexus. Pleural effusion may be caused by obstruction of the inferior vena cava by lymphadenopathy in the lower mediastinum or to infiltration of the pleura. Bucky films may reveal retrocardiac nodes. Irradiation does not produce prolonged improvement in this relatively late stage. Rarely parenchymal infiltration of the lung will produce a miliary appearance or that of falling wet snow. Treatment may produce pronounced improvement as the invasion is that of lymphoid cells at the junctions of the smaller branches of the bronchi. When Hodgkin's or lymphosarcoma are suspected, therapy may be expected to shrink from 30 to 100 per cent of the tumor within three to four weeks after a well-planned course of treatment. In relatively acute lymphoblastoma, the time interval between apparent onset and death varies from six months to three years, but the majority have a relatively subacute form in which disease process extends from three to six years. — *Roentgen Treatment for Hodgkin's Disease and Lymphosarcoma of the Chest, A. U. Desjardins, Dis. of Chest, November-December, 1945, 11: 565.*—(K. R. Boucot)

Neurogenic Tumors.—In the years since Pancoast first described the syndrome of superior pulmonary sulcus tumor, it has become evident that the entity of pulmonary apex associated with rib or vertebral destruction, pain around the shoulder and down the arm, and Horner's syndrome are produced by a variety of malignant neoplasms most of which are primary carcinomata of the apex of the lung. This interest has overshadowed to some extent the fact that growths of a benign nature, mostly neurogenic in origin, show a tendency to develop in this same location. These have been described as mediastinal in origin since they are prone to originate from intercostal nerves close to

the spine or from paravertebral ganglionic chains in the posterior mediastinum. As the tumor enlarges it protrudes into the lung field and its chief clinical and roentgenological manifestations may be pulmonary rather than mediastinal. The incidence of all benign intrathoracic tumors is low. In Blades' review there were 233 cases of teratoid tumors, all but 3 of which originated in the anterior mediastinum. The next most frequent tumors were those of the neurogenic group of which there were 135 reported cases, the majority arising in the posterior mediastinum or along its margins. All the remaining types were rare—32 fibromata, 14 tumors arising from bone or cartilage, 15 cysts, 34 lipomata, 5 xanthomata. Clinically, neurofibromata tend to develop to considerable size without significant symptoms until there ensues encroachment upon or displacement of some vital structure. Discovery is often accidental on routine X-ray examination. When these tumors are limited to the apex, in contrast to malignant tumors, occurrence of Horner's is rare as is pain radiating down the arm. Lateral, oblique and stereoscopic films show small tumors to be located posteriorly and in close association with the ribs and spine. No bone destruction is evident though pressure erosion of one or more ribs may be present. In contradistinction to malignancies of the pulmonary apices, the outstanding symptoms are due to irritation or damage of the upper intercostal nerves, brachial plexus and thoraco-cervical sympathetic ganglionic chain. Substernal thyroids, aneurysms, thyroid and thymic tumors, neoplasms of the paratracheal or anterior mediastinal nodes must be differentiated. Surgery is indicated even though the tumor is small and asymptomatic because of the inherent tendency to malignant degenerations, the probability of increase in size with consequent increased surgical difficulties, and the possibility of mistaken diagnosis. Two cases are reported in which operative removal of the tumor revealed the diagnosis of neurofibroma in one, neurofibrosarcoma of low grade malignancy in the

other. Two other cases are presented that have been under observation for periods of six and seven years, respectively, but in whom there is no histological proof of diagnosis.—*Tumors at the Pulmonary Apex, L. W. Paul, Dis. of Chest, November-December, 1945, 11: 64S.*—(K. R. Boucot)

Lung in Tuberous Sclerosis.—Tuberous sclerosis is a hereditary and congenital disease, due to a disturbance in the development of the mesenchymal tissue. It manifests itself in childhood or youth and is fatal at a fairly early age. All kinds of fibromatous skin tumors occur; *adenomata sebacea* and subungual fibromata are thought to be pathognomonic. A motley collection of tumors may occur in various organs, such as heart, liver, spleen, kidneys, eyeground, (phakoma) and, above all, in the brain. They consist of embryonal cells of muscular, adipose, connective or vascular tissue. The *adenomata sebacea* are nowadays regarded as *naevi* with partly embryonic cellular form and some are pure angiomas. The angiomatic component is often conspicuous also in other tumors. No changes were noticed in the lung until one of the authors, G. Berg (1938), and G. Berg and G. Vejlsens (1939) published a pertinent case with simultaneous cyst-like pulmonary changes. An investigation of this patient's family was carried out by Berg in 1938 to 1940. A woman, 30 years old, became acutely ill with a spontaneous pneumothorax which relapsed several times during the subsequent years. The only symptom was increasing dyspnea; she died from asphyxia more than two years after the onset of her symptoms. The first roentgenogram revealed a total left-sided pneumothorax and two bean-sized subpleural translucencies, interpreted as emphysematous bullae; in the right lung there was a delicate net-like pattern caused by smaller round translucencies. Shortly before death a similar pattern with translucencies was seen in both lungs. At autopsy, both lungs were dotted with evenly distributed small bullae; the cut-surface resembled a sponge and showed

that the lung tissue was interspersed with small cavities embedded in a thick, firm tissue. Microscopically, the walls of these cysts had no epithelial covering and consisted of connective tissue and blood vessels; but the most prominent element was smooth muscle tissue having the unmistakable character of tumor tissue of embryonic type. There were also tumorous changes, for instance in the brain, spleen and kidneys, similar to those in tuberous sclerosis. The younger sister, then 20 years old, had *adenomata sebacea*, subungual fibromata and a slight, limited sclerosis in the cranium. The roentgenogram showed a fine net throughout both lung fields, due to numerous, closely related emphysematous blebs. Fifteen months later a gradually increasing dyspnea developed; a wart-like tumor was found in the right eye-ground; a tumor in the recto-vaginal wall was extirpated and diagnosed as a myoma rich in vessels of embryonic character. The patient died after a period of three and a half years of observation which, on one occasion, revealed a small spontaneous pneumothorax but never other essential changes in the lung. The autopsy showed, beside the neoplastic changes in the skin, kidneys, cerebrum, that the lungs were dotted with cysts. Microscopically, the alveoli were mostly filled with blood and hemosiderin-laden cells. The transformation of the lung tissue consisted principally of (1) a fibrous enduration, rich in vessels, in a partly angiomatous formation, (2) an extensive, angiomatous formation, not localized in distinct foci or nodes and (3) a large number of cystoid formations. (These three changes are described in detail.) In a younger brother, 28 years old, a few symptoms of tuberous sclerosis, but no pulmonary changes, were detected, and one of his children had *adenomata sebacea*. Examination of his two older children, as well as of his youngest brother, gave negative results. Roentgenograms of the lungs of the father and his oldest son were normal. The authors "are of the opinion that the pulmonary changes constitute a part phenomenon of the blasto-

matosis which occurs in cases of tuberous sclerosis of the brain." They stress "the great abundance of embryonal and malformed vessels . . . which indicates a certain connection between *Morbus Recklinghausen*, tuberous sclerosis and hemangiomatosis."—*Pulmonary Alterations in Tuberous Sclerosis*, G. Berg & A. Nordenskjöld, *Acta med. Scandinav.*, 1946, 125: 428.—(O. Pinner)

Injury of Thoracic Duct.—It has been shown both clinically and experimentally that the thoracic duct can be ligated without untoward result. Collateral circulation apparently develops quickly so that no significant rise of pressure in the lymphatic system develops. Injury to the thoracic duct which is unrecognized and permits the continuous loss of chyle from the body, either externally or into the pleural cavity, carries a high mortality. Dehydration and inanition are common under the circumstances, as it has been shown that lymph flow in the thoracic duct ranges from 60 to 190 cc. per hour. Chylothorax due to injury of the thoracic duct is rare. Only 62 cases have been reported, including the one here published. If the thoracic duct is injured low in the chest, right chylothorax may result, but if the injury is higher up, or in the neck, left chylothorax occurs, due to the crossing over of the duct from right to left in the upper chest. The present case is that of an officer who was wounded by a bullet which entered the upper back and left the body just above the left clavicle. He had a hemopneumothorax on admission and he had to be aspirated twice daily to relieve respiratory distress. After a few days the fluid became less bloody and the characteristic milky nature of the fluid was first noted. Because of the patient's obvious downhill course, operation was decided upon. Exposure of the structures at the root of the left neck demonstrated the tear in the pleura and the severed end of the thoracic duct. Following ligation of this the patient made a remarkable recovery. It is well to remember to be on the look-out for the thoracic duct in operations on the neck during dissection for malignancy, or when a Smith-

wick operation for hypertension is performed on the right side of the thorax.—*Injuries of the Thoracic Duct*, R. H. Lee, *Arch. Surg.*, October, 1946, 53: 448.—(H. Marcus)

Chylothorax.—This is a rare entity. There are only meager data available. These suggest that the prognosis in the acquired type is better than that in the congenital type. There is no record of successful surgical correction of chylothorax in infancy. A case report is presented of an 8-week-old white girl with a history of irregular breathing for one week before admission. Four days before admission while being fed, it was noted that she was in distress and was breathing with difficulty. There was rapid respiration, wheezing and retraction of the upper abdomen and supra-sternal areas. Her color was good and she had no fever. The following day, clinical and roentgenological examinations revealed fluid in the right chest. Thoracocentesis revealed milky fluid. On hospital admission she was apparently normal except for rapid, somewhat labored breathing. A flat percussion note was present on the right, both anteriorly and posteriorly, with a shift of the heart to the left. The respiratory rate was 60 per minute. Repeated thoracocenteses were necessary. The fluid was sterile. Specific gravity ranged between 1.008 and 1.130. Cholesterol on one occasion was 102 mg. per cent, total fat 1,435 mg., protein 3.274 g., and 2,245 cc. chyle were removed before the fistula closed. The course was afebrile throughout. The white count ranged between 4,900 and 8,000 with a normal differential. Sulfadiazine was given prophylactically. Cessation of leakage of chyle into the thoracic cavity was coincidental with onset of mild diarrhea. Yater places non-traumatic chylothorax as more frequent in occurrence than traumatic. Neoplasm and inflammatory lymph nodes, including tuberculosis, constitute the commonest causes of nontraumatic chylothorax. An excess over calculated normal food requirement is advisable. Of 13 cases of acquired chylothorax, healing occurred in more than 50 per cent.—*Spontaneous Chylothorax in Infancy: Prognosis*

and Management, E. H. Watson & L. F. Foster, *Am. J. Dis. Child.*, July, 1946, 72: 89.—(K. R. Boucot)

Hemorrhagic Pleurisy and Leukemia.—Case history of a 17-year-old patient with pulmonary tuberculosis of the left lower lobe treated with pneumothorax of four years' duration after which time a hemorrhagic effusion appeared in the pneumothorax space. Blood count revealed findings indicative of myelogenous leukemia. Bleeding and coagulation time were normal. Enlargement of liver and spleen appeared several months later. It is thought that the hemorrhagic effusion in this case is due to leukemia. The occurrence of left pleurisy in leukemia is usually attributed to perisplenitis and its extension into the surrounding structures. However, in the present case there was no demonstrable enlargement of the spleen at the time when pleural effusion occurred.—*Pleurésie hémorragique dans un pneumothorax, signe révélateur d'une leucémie myéloïde insidieuse jusque-là méconnue*, W. Jullien & J. L. Jullien, *Rev. de la tuberc.*, 1944-45, 9: 288.—(V. Leiles)

Typhoid Empyema.—Empyema is one of the rarest complications of typhoid fever. The authors report the case of a 12-year-old white girl admitted to Children's Free Hospital, Louisville, Kentucky, on June 24, 1942. Onset of illness was twenty-four days prior to admission with weakness and fainting. The following day chills, fever, and vomiting developed and persisted until admission. Two weeks following the onset, stools became diarrheal and three days before admission contained blood. Four days before admission there was severe pain accompanied by hemoptysis. Shortly before admission the patient and her family had been visiting in the "mountains." Physical examination revealed an acutely ill child crying with pain in the right chest. There was a definite lag on the right with impairment to percussion posteriorly, especially below the level of the second rib. Breath sounds were diminished and tactile fremitus was absent in this area. Mild ab-

dominal distension was present and the temperature was 102.4° F., pulse 112, respirations 30, red cells 5,010,000 with 97.4 per cent of hemoglobin, white cells 17,200 with 57 per cent polynuclears, 27 per cent lymphocytes, 2 per cent monocytes, 14 per cent stab forms. Albumin one-plus and 5 to 15 white cells per field. Chest X-ray film revealed homogeneous density in the base of the right lung. Aspiration yielded a small amount of thick bloody material from which *B. typhosum* was isolated. On June 26 and 29, blood serum agglutinated *B. typhosum* in dilution of 1:1280, but cultures of whole blood were negative for the organism. High caloric and high vitamin fluid diet were given, supplemented by infusions of dextrose and isotonic sodium chloride solution. Hemoptysis and vomiting continued. Fever was continuous, at times to 105° F. Despite repeated transfusions, by July 1st the red cell count was 3,350,000 with 70 per cent hemoglobin. Urine culture at this time was positive. Stool cultures became positive. On July 3rd, stool, sputum and fluid aspirated from chest all contained *B. typhosum*. Blood culture was negative. On July 6, 250 cc. of purulent, gaseous, chocolate-colored material with a fecal odor were obtained by thoracocentesis. The aspiration was terminated because of persistent cough. The organism was obtained on culture of the pleural fluid. On July 8th, 500 cc. pleural fluid were aspirated, but again termination of the procedure was necessitated because of persistent cough. On July 10th, 350 cc. more were aspirated; because of persistent accumulation of fluid, open drainage was done, 500 cc. being obtained at the time of operation. A bronchopleural fistula was demonstrated at the time of operation. A soft rubber catheter was inserted. Postoperative course was stormy with gradual improvement. Patient became afebrile and has remained well since.—*Typhoid Empyema: Report of a Case with Recovery*, E. P. Scott & J. W. Bruce, *Am. J. Dis. Child.*, March, 1946, 71: 277.—(K. R. Boucot)

Hiatus Hernia.—A progressive herniation of the greater part of the stomach through the hiatus may lead to gastric volvulus, manifested clinically by phenomena of mediastinal compression and/or by occlusion of the pylorus and circulatory disturbances of the stomach. This type of hiatus hernia is not included in either of the best known classifications (Akerlund and Harrington). Considering this variety, the following classification is suggested: (1) thoracic stomach, due to shortness of the esophagus; (2) true hiatus hernia with penetration of the fundus through the hiatus, while the cardia remains in normal position; (3) the small hiatus hernia, corresponding to Harrington's hiatus insufficiency; (4) hiatus hernia with normal esophagus and elevation of the cardia; and finally (5) hiatus hernia with gastric volvulus, which may be considered as the most advanced stage of the true hiatus hernia.—*Las hernias del hiato esofagico del diafragma: Su clasificacion*, R. C. Ferrari, *Prensa med. argent.*, August, 1946, 33: 1586.—(L. Molnar)

Diaphragmitis.—Hedblom's syndrome is defined as acute primary myositis of the diaphragm manifested clinically by ponopnea (pain on inspiration) on affected side, limitation of mobility of lower chest wall and tendency to flaring out of costal margin with each inspiration. There may be pain in the upper abdominal quadrant or in the homolateral shoulder. Roentgen picture reveals a tendency of the involved diaphragm to rise and to have limited or absent mobility. Mobility may be resumed, but flattening remains. Diaphragmatic pleurisy due to involvement of the pleura or lung or to subphrenic peritoneal irritation are described as secondary "diaphragmitis" in contradistinction to Hedblom's syndrome which is primary in the muscle fibers with extension to the pleura above and to the subphrenic area below. The author has collected 42 cases in his own practice. Diagnoses, in some instances, had been made as diaphragmatic pleurisy, basal pneumonia, acute cholecystitis or acute appendicitis. Five case reports with roentgenograms

are presented. There is acute inflammation in the muscle and it may be limited to the muscle bundles or may extend to the serous surfaces. Acute cases may be characterized by a sudden onset with pain on the involved side which is localized over the costal margin and ipsilateral shoulder. Cough may or may not be present.—*Acute Primary Diaphragmitis (Hedblom's Syndrome) M. Joannides, Dis. of Chest, March-April, 1946, 12: 89.*—(K. R. Bouco!)

Mediastinal Emphysema.—Mediastinal emphysema may occur following chest and neck trauma, surgical procedures on the neck and thorax, positive pressure anesthesia and pneumothorax. It may also occur in the course of any pulmonary infection which is accompanied by severe coughing spells. Recently, attention has been called to the spontaneous occurrence of this clinical picture. The spontaneous and secondary types differ little in their clinical manifestations; the latter are more apt to result in severe symptoms. Pneumothorax is frequently associated with mediastinal emphysema; the pneumothorax is usually small and occurs over the apex of the lung. Mediastinal emphysema may be the precursor of spontaneous pneumothorax in a considerable proportion of cases. The primary source of air in mediastinal emphysema is a ruptured alveolus. The air can then spread in two directions: to the periphery of the lung with formation of emphysematous blebs and a pneumothorax; or subpleural air may dissect back to the hilum and then into the mediastinum. Air from a ruptured alveolus can also move along the perivascular sheaths to the mediastinum. Mediastinal air may spread upward producing subcutaneous emphysema; it may also dissect downward retroperitoneally as far as the scrotum. This air may be under sufficient pressure to collapse the pulmonary and systemic veins. The two outstanding clinical features are chest pain and a characteristic sound synchronous with the heart beat. The pain is usually first noted in the left upper or mid-chest; subsequently, it

may become substernal and radiate in various directions, closely simulating anginal pain. The pain is aggravated by motion and breathing. The bizarre sounds heard over the pre-ordium are diagnostic and may come on a short time after the onset of the pain. These sounds are caused by the heart contracting against bubbles of air and have been variously described as clicking, crackling and crunching. They vary with respiration and the position of the patient. After several hours the sounds may disappear entirely. Within twenty-four hours, subcutaneous emphysema may appear. Chest X-ray films may reveal a thin line of air parallel to the cardiac border on either side. Electrocardiograms, blood counts and sedimentation rates are usually within normal limits. Acute pericarditis and acute coronary occlusion are the main differential problems. Electrocardiographic changes, fever and leucocytosis will usually serve to differentiate these two conditions from mediastinal emphysema. The pain in coronary occlusion is usually not affected by respiration. Treatment of mediastinal emphysema consists of bed-rest, analgesics and sedatives. Bed-rest of several weeks' duration is especially important since there is a definite tendency to recurrence. In severe cases, with subcutaneous emphysema and signs of mediastinal obstruction, surgical incision and direct aspiration of air may be required. Acute cellulitis of the mediastinum is a potential complication and prophylactic chemotherapy is advisable particularly in the presence of a respiratory infection. Seven case histories are detailed. In one, the mediastinal emphysema was associated with bronchial asthma; 6 were of the spontaneous type. In 5 patients, the condition recurred. All 6 spontaneous cases developed an associated pneumothorax.—*Acute Mediastinal Emphysema, B. M. Schwarz, G. H. McLroy & H. H. Warren, Ann. Int. Med., October, 1946, 25: 663.*—(H. R. Nayer)

Mediastinal Cysts.—Since 1870 when von Wyss first reported a mediastinal cyst lined with primitive esophageal mucosa, 74 cases of

intrathoracic cysts of foregut origin have been reported in the literature. Of these, 35 were lined with epithelium derived from primitive foregut in the region of the lung bud or from the lung bud itself, 12 with primitive esophageal epithelium, 15 with gastric mucosa, 4 with intestinal mucosa and 8 with mucosa of mixed types. A 9-day-old white boy was transferred from the nursery because of several attacks of dyspnea, tachypnea and cyanosis during the previous two days. The infant nursed poorly and failed to gain weight. He was placed in an oxygen tent. Cyanosis and dyspnea developed on removal from the tent. Three days after transfer, massive atelectasis with obstructive emphysema at the bases was noted roentgenologically. Dyspnea and cyanosis recurred despite oxygen therapy. The infant died seven days after transfer. Autopsy revealed a completely atelectatic left lung, the thoracic cavity being half-filled by a tense, cystic oval mass containing clear straw-colored watery fluid. Section of the cyst wall revealed in one area mucosa resembling that of the intestine; in another area the mucosa resembled that of the stomach. Theories regarding embryological origin are presented, the authors outlining their own conviction that all these cysts are derived from the foregut at or near the region of the lung buds where gastrointestinal and respiratory tract constituents are rapidly developing in close proximity. Pinching off of single cells or similar or dissimilar cells takes place. The descent of the pericardium and the natural lengthening of the gastrointestinal tract and the growth and development of the respiratory tract are partly responsible for the migration and final position of these cells. In esophageal cysts separation of cells probably occurs at a more advanced stage; hence, migration is not so pronounced and the cysts often develop within the wall of the esophagus itself. Separation of cells forming bronchogenic cysts may occur early or late. Grossly all these cysts resemble each other. Classification depends on the histological character of lining mucosa and wall. Thirty-five cases of bronchogenic mediastinal cysts have been reported. There were 39

cases of esophageal, gastric, enteric and mixed mediastinal cysts. Eighteen of these 39 cases were found to have other congenital anomalies. The symptoms of mediastinal cysts of primitive foregut origin are primarily the results of mechanical pressure on adjoining structures. They may be present at birth or shortly thereafter. However, especially in esophageal cysts, they may not appear for years, if at all. Commonest symptoms are dyspnea, cyanosis, and cough appearing soon after birth and may be intermittent. Roentgenological examination may fail to outline the cysts. In such instances, aspiration of the cyst and introduction of a radiopaque substance should be attempted. Treatment is always surgery.—*Congenital Mediastinal Cysts of Foregut Origin, J. L. Olenik & J. W. Tandatnick, Am. J. Dis. Child., May, 1946, 71: 466.*—(K. R. Boucot)

Treatment of Suppurative Mediastinitis.—This condition has been, until recent years, a disease accompanied by a high mortality rate. Author reports 7 cases with 7 recoveries. The symptoms of acute suppurative mediastinitis develop within one to six hours of an esophageal injury. The earliest symptom in all cases was pain on swallowing, and was noticed in some degree from the first fluids taken after injury. Physical signs observed in the cervical region were tenderness, fulness and edema along the sternomastoid muscle. Those with lower esophageal leakage had epigastric tenderness and spasm. All cases showed a rapid temperature elevation and increased leucocyte count from 13,000 to 31,000 within twenty-four hours. A transient but treacherous improvement may induce in the physician a dangerous impression that recovery has begun. Any patient suspected of having suffered an esophageal perforation should be examined promptly by X-ray. It is imperative that the diagnosis be confirmed or excluded promptly. If a perforation is present it may be demonstrated by extravasation of the barium mixture and immediate drainage must be instituted. In treatment the primary requirement is the prompt establishment of dependent drainage and gastros-

tomy. The site of drainage is determined by the level of the esophageal perforation and the location of the mediastinal abscess. In all cases the infection was found to extend into the upper thorax. In each of these cases the mediastinal abscess was packed loosely with dry gauze. One catheter was placed for constant drip of penicillin or sulfanilamide solution. Another catheter was placed on suction with its inner end within the wound in the chest wall. All patients kept in the Trendelenburg position for five days. The irrigations discontinued and gauze packing removed on the fifth day and a soft rubber tube inserted for maintenance of drainage. Rubber tube gradually shortened as drainage decreased. The gastrostomy is essential to put the esophagus at rest until the perforation has healed. Food, vitamin and water intake was kept high and chemotherapy used in massive dose until after all signs of systemic infection had subsided.—*Acute Suppurative Mediastinitis*, R. Adams, *J. Thoracic Surg.*, October, 1945, 15: 586.—(W. M. G. Jones)

Surgery in Congenital Heart Disease.—Anastomosis of the subclavian or innominate artery to either the right or the left pulmonary artery for the relief of anoxemia due to pulmonary stenosis or pulmonary atresia was advised by Blalock and Taussig in 1945. Use of the innominate artery for such an anastomosis entails the hazard of an inadequate supply of blood to the brain. Experimental work on dogs showed that clamping off the aorta completely for any considerable length of time leads to paralysis of the hind legs in a fair number of cases. A procedure is advised by which an anastomosis between the aorta and the pulmonary artery can be performed while a substantial amount of blood is flowing through the aorta. This was made possible by a new type of clamp. The two flanges of this clamp encircle the aorta and, when closed, pinch off a small portion of the aorta to allow room for an anastomosis. The technique of the operation is described in detail. This operation was performed on 3 children suffering from congenital heart disease diagnosed as tetralogy of Fallot.

One child died thirty-six hours after the operation. The other 2 children benefited tremendously by the operation. There was marked decrease in cyanosis, red blood cell count and hemoglobin immediately following the operation.—*Anastomosis of the Aorta to a Pulmonary Artery: Certain Types in Congenital Heart Disease*, W. J. Potts, S. Smith & S. Gibson, *J. A. M. A.*, November 16, 1946, 132: 627.—(H. Abeles)

Pulmonary Embolism.—In experimental pulmonary embolism a peculiar state of shock develops, characterized by hypertension in the lesser circulation, hypotension in the major circulation and vasoconstriction in both. It is due to a disturbance in the distribution of blood between the arterial and venous system, produced by a spasm of the pulmonary vessels. This spasm is independent of sympathetic innervation; it persists after bilateral sympathectomy. The peripheral vasoconstriction is attributed to the diminution of the cardiac output.—*M. L. Binet & M. Burslein, Presse méd.*, October, 1946, 633.—(V. Leites)

Dilatation of Pulmonary Artery.—Isolated congenital dilatation of the pulmonary arterial tree without other developmental anomalies with the exception of hypoplasia of the aorta is extremely rare. A 41-year-old white woman was seen who had had dyspnea and palpitations for the past seven years. Three weeks prior to her hospital admission she developed fever and chills. On physical examination she showed cyanosis of finger tips and toes, a systolic thrill over the precordial region, enlargement of the heart to the right and a systolic murmur at the left sternal border. Fluoroscopy revealed a dilated pulmonary conus, pulsation of the pulmonary vessels and hypertrophy of the right ventricle. On blood culture *Streptococcus viridans* was found. The clinical diagnosis of patent ductus arteriosus was made. An operation was performed to tie off the ductus arteriosus. The patient died in the operating room. The autopsy revealed a tremendous hypertrophy of the right side of the heart. The aorta was

small. The pulmonary artery and its branches were enlarged and showed arteriosclerosis. There was thrombosis in some of the large and medium sized pulmonary arteries. There was no communication between pulmonary artery and aorta. There was no fibrosis nor emphysema of the lungs, but a moderate degree of atelectasis. The presence of a large pulmonary artery and a small aorta is apparently due to an unequal division of the *truncus arteriosus communis*. The arteriosclerotic changes are believed to be due to the abnormal stretching forces in the wide artery.—*Congenital Dilatation of the Pulmonary Arterial Tree*, M. M. A. Gold, *Arch. Int. Med.*, August, 1946, 78: 197.—(G. C. Leiner)

Superior Vena Cava Obstruction.—Two case reports of mediastinal tumors leading to obliteration of the superior vena cava. In the first case a primary pulmonary sarcoma had invaded the superior vena cava and the right auricle. Marked collateral circulation had developed between the umbilical and epigastric veins. There was engorgement of the jugular veins, dyspnea, cyanosis, unilateral edema of the arm and breast and bilateral pleural effusions. In the second case a carcinoma of the esophagus had penetrated into the superior vena cava which became obstructed 3 cm. above the right auricle. Clinically there had been no collateral circulation nor edema, but considerable dyspnea, cyanosis and a tracheal tug. The neoplasm had not produced marked narrowing of the esophagus; the growth had been eccentric with formation of a huge mediastinal tumor.—*Oblitération de la veine cave supérieure et tumeur du médiastin*, R. Lutembacher, *Presse méd.*, October, 1946, 643.—(V. Leites)

Superior Vena Cava Obstruction.—Three cases are reported. All showed the classical clinical picture. The onset was gradual. A noteworthy fact is that there was swelling of the head and neck but not of the upper extremities. The venous pressure in the area drained by the superior vena cava was ele-

vated. Application of a tourniquet to the chest caused increased elevation. The circulation time was prolonged. Roentgenograms showed slight widening of the superior mediastinal shadow. The conclusion was reached that the obstruction was due to chronic mediastinitis. A review of the literature indicates that mediastinitis is attributable to: (1) tuberculosis, (2) syphilis and (3) undetermined. The author wonders whether the presence of calcified lymph nodes or a positive serological test for syphilis are *per se* adequate evidence for a specific etiology. The 3 reported cases do not shed any light on a possible etiological cause. Some temporary relief is afforded by venesection. Antisyphilitic therapy is beneficial in suitable cases. Mediastinotomy with the objective of cutting the scars is of questionable value.—*Superior Vena Canal Obstruction Due to Chronic Mediastinitis*, O. Tubbs, *Thorax*, December, 1946, 1: 247.—(A. G. Cohen)

Tuberculosis and Empire Responsibility.—Sixty million people live in the British Colonies exclusive of the Dominions. Exhaustive plans for their welfare do not include tuberculosis. A survey on *Empire and Colonial Tuberculosis* by Prof. Lyle Cummins asserts that the number of victims of such dreaded diseases as bubonic plague and cholera rank far behind those of tuberculosis. This is true of other much publicized tropical diseases. Cummins thinks the difference between European and non-European natives in their reaction to tuberculosis is a difference in the speed at which immunity takes place. In civilized man, relative immunity is acquired with fair rapidity. In the primitive, it develops slowly; in the meantime, serious and fatal disease may have taken place. Native peoples are becoming more industrialized, and hence the hazard of tuberculosis will be increased.—*Tuberculosis: An Empire Responsibility, Annotations*, *Brit. M. J.*, November 9, 1946, 4479: 700.—(R. W. Clarke)

Tuberculosis in Trinidad and Tobago.—Inhabitants of these islands are descendants of

African slaves, workers from India, Spanish and French settlers, a total of half a million. Africans predominate in the town, Indians in the rural areas. Tuberculosis mortality has declined from 275 per 100,000 in 1898 to 93 at present. The incidence of non-pulmonary tuberculosis is low; little milk is used; there is a higher death rate in the towns. Africans tend to present more acute than chronic disease; the Indians have less disease with a tendency towards chronicity. Recommendations in the report of the Colonial Office conducted by W. Santon Gilmour consist of a chief tuberculosis officer, a medical superintendent, a sanatorium-hospital of 268 beds, two chief clinics, a long-term policy of better housing and slum clearance.—*Tuberculosis in Trinidad and Tobago, Annotations, Brit. M. J., August 31, 1946, 4469: 308.*—(R. W. Clarke)

Tuberculosis Mortality in France.—Tuberculosis mortality in 18 large French towns in 1945 was compared with the average rates during the period 1934 to 1936. Causes of error in the evaluation of the available statistical data are discussed. All reservations made, the results of the study seem to indicate a notable decrease of tuberculosis mortality during this period, a fact considered paradoxical, but for which no adequate explanation is given.—*La mortalité par tuberculose dans les grandes villes françaises en 1945, P. Boulanger, F. de Cambrun & M. Moine, Bull. Inst. Nat. d'hyg., July-September, 1946, 1: 161.*—(V. Leites)

Social Factors and Tuberculosis.—A comparative study is made of tuberculosis mortality in France between the years 1925 and 1942. In the first years of life, tuberculosis mortality showed a decline of 45 per cent in 1936 as compared to 1925. An increase of 80 per cent took place between 1936 and 1942. Both sexes are equally affected. The tuberculosis mortality of adults showed marked differences according to sex. Thus, the mortality of males between the ages of 20 and 24 declined by 36.5 per cent from 1925 to 1936, as compared to a decline of 42 per cent

in women of the same age. This age group shows an increase in mortality during the war years as high as 41 per cent for males and 10.5 per cent for females. The highest rise in mortality (57 per cent) was found in men in the age group 30 to 34 from 1936 till 1942. The corresponding rise for females was 15 per cent. The marked difference in the mortality rate of the two sexes cannot be explained by factors which are identical for males and females, such as tuberculosis control, treatment, housing and food shortage, etc. Working conditions leading to excessive fatigue are mainly held responsible for the high tuberculosis mortality in males. Another factor increasing this rate is the death of repatriated prisoners of war having contracted tuberculosis during captivity.—*La tuberculose et le terrain social, P. Boulanger, Rev. de la tuberc., 1946, 10: 266.*—(V. Leites)

Tuberculosis in Industry.—To the employer responsible for the welfare of his staff, who must measure efficiency in terms of cost and production, infection and reduced working capacity are two features of tuberculosis that cause him to look upon the employment of tuberculous personnel with anxiety. Primarily, contact with the tubercle bacillus is occurring in the later age groups with the highest incidence of tuberculosis. The discovery rate has increased so that the rise in incidence is not a true rise in the rate of development. So-called harmless dusts may indirectly spread tuberculosis by causing chronic catarrh in an individual with an undiscovered active lesion, the so-called catarrh being responsible for increased cough, and the droplets thus produced bearing tubercle bacilli from the unsuspected active lesion. In offices where a number of cases of pulmonary tuberculosis had occurred, sickness due to colds was high, and also methods for removing of dust were inadequate. Light work under bad conditions may be more harmful than heavy work under good conditions to those having recovered from tuberculosis or those who are potential patients. Irritating fumes may produce an inflammatory reaction

of the lung favoring the development of tuberculosis. In the past, too much time and skill have been wasted on the impossible task of restoring the advanced case to health. It is urged that more time and better rehabilitation, including the granting of financial assistance, be given to those recovering from tuberculosis. For those unable to find suitable work, special workshops are urged.—*Tuberculosis in Industry, F. Heaf, Brit. M. J., December 28, 1946, 4486: 975.*—(R. W. Clarke)

Marital Tuberculosis in Amsterdam—Data were collected during the years of 1934 to 1938 at the Amsterdam Tuberculosis Dispensary from 790 people whose spouse showed tubercle bacilli in sputa or gastric contents; 327 of them were followed until 1942. All patients were laborers or belonged in the lower middle class income group. All cases, in which there was any doubt about the marital origin of the tuberculosis, were eliminated. The prevalence of marital tuberculosis was 6.8 per cent in women and 3 per cent in men, average of 4.9 per cent. These figures were compared with the average morbidity of tuberculosis in married citizens of Amsterdam, whose spouses did not suffer from tuberculosis. The morbidity of marital tuberculosis in men was 2.18 per cent, morbidity without conjugal infection was 0.44 per cent. In women these figures are respectively 5.18 and 0.5 per cent. Conjugal contamination revealed in men to a fivefold, in women to a tenfold morbidity. In women under the age of 30 years, marital tuberculosis was found twice as frequently, as in women past that age. Influence of pregnancy and child birth could not be established with certainty. The results of the tuberculin tests before the beginning of the contaminating contact in marriage, were unknown in the majority of cases. Under unfavorable conditions (housing, feeding, income), twice as many cases of marital tuberculosis occurred as under favorable conditions. Thrice as many cases of conjugal tuberculosis were found in the marital partners in whose family tuberculosis patients were known, as in those coming from tuberculosis-free families. Over

58 per cent of the cases of marital tuberculosis had positive sputa. Mortality was 40 per cent. Routine examinations of spouses of patients with open tuberculosis is recommended. This should be pursued for two years after the end of the contact.—*Marital Tuberculosis in Amsterdam, J. Meyer's, Gravenhage, 1946, (a monograph).*—(K. van Leeuwen)

Causes of Death in Psychopathic Hospital.—In a survey of the causes and incidence of death in an acute psychopathic hospital, 332 persons died of 3,374 patients admitted. Of 2,547 non-senile patients, 101 died, cardiovascular disease being the most common cause. Alcoholism and general paresis were the next most common causes, 10 per cent died of "agitation" of unknown etiology and 5 per cent of tuberculosis.—*Analysis of the Incidence of Death in an Acute Psychopathic Hospital, L. Madow & J. Stouffer, Am. J. M. Sc., October, 1946, 212: 471.*—(G. F. Mitchell)

Tuberculosis in Sanatorium Personnel.—The control program at the Tuberculosis Sanatorium of Huipuleo, Mexico, is as follows: only tuberculin-positive persons over age 20 are accepted for employment; a roentgenogram is taken at the time of employment and annually thereafter; a complete physical examination is given, and repeated with chest X-ray examination on occurrence of any illness regardless of the apparent lack of relationship to tuberculosis. Personnel is classified according to exposure into three groups: (1) highly exposed (doctors, nurses, maids, orderlies, etc.); (2) incidental contact (pharmacists, painters, etc.); (3) never exposed (cooks, some clerks, etc.). Over an eight-year period, 492 individuals worked at the sanatorium for periods of time varying between several weeks and eight years. Among the 357 highly exposed individuals, only 2 maids, one gardener and one orderly developed reinfection type tuberculosis. This represents an incidence of 1.1 per cent, which is lower than that in the general population of Mexico City. None of the other two groups developed demonstrable lesions. Tubercle bacilli were never demon-

strated in the sputum of the 2 maids, but in that of the orderly.—*Tuberculosis among Sanatorium Personnel*, D. G. Alarcon, *Dis. of Chest*, July-August, 1946, 12: 336.—(K. R. Boucot)

Readaptation of the Tuberculous.—Readaptation of the ex-sanatorium patient to the outside world is a problem that resembles the readaptation of the demobilized service man. Adult education or vocational guidance and occupational therapy, patient organizations and activities both within and outside the sanatorium, aid in this problem.—*Réadaptation et tuberculose*, G. Descarreaux, *Laval méd.*, January, 1947, 12: 67.—(E. Bogen)

Bed Usage in Tuberculosis.—In view of the present limited supply of beds for tuberculous patients it is questionable whether minimal or far advanced cases should be hospitalized. The apparently irreconcilable views of the "private chest specialist who is interested primarily in the individual patient" and "of the public official who is concerned with the health of the entire community . . . are easily made compatible if certain fundamental concepts are understood." Both "must agree that a bed occupied by a person who could be supervised adequately as an ambulatory case is a bed lost to a patient whose disease could be arrested and prevented from spreading." In any community the morbidity and mortality rates, the quantity and availability of hospital beds, clinics, nursing, medical, social and other professional services, the number and distribution of physicians trained in chest diseases are important factors in determining the local problem and instituting a sound program; certified laboratories must be available. "What is the purpose of hospitalization of the tuberculous— isolation or treatment?—Does the community with a scarcity of beds, benefit more through the hospitalization of minimal inactive cases or of advanced infectious cases? [This is an obvious *petitio principii*. The dilemma is not between "minimal inactive cases and advanced infectious cases" but between minimal active cases and more or less

equally infectious but advanced and frequently hopeless cases.—Editor]—Should communities develop preventoria for children who are heavily exposed and certain to become infected, but do not have yet clinical disease?" The answers are: "The protection of the health of the community takes precedence over the health of any individual.—The positive sputum case must be hospitalized to prevent spread of the disease; the earlier the case is found the better.—Hospitalize the infectious adult source and thereby remove the danger of infecting children in the home. It is easier and more economical to hospitalize one parent than three or more children." The positive sputum cases should be separated into those with little hope of recovery and those with remediable disease. "Hospitalize first the remediable positive sputum group. The irremediable . . . case could be isolated in the general hospital until the terminal episode." If this is impracticable, "the hopeless case should be cared for in the home under the best possible isolation technique, supervised by a public health nurse. Advanced positive sputum cases already in sanatoria but not benefiting from treatment should be . . . replaced by positive . . . cases that have chances for recovery. . . . The minimal case with . . . active disease should be given equal opportunity with the advanced remediable case, so that progression of the disease can be prevented." Minimal cases with no tubercle bacilli "can be supervised as ambulatory patients in the clinics and the offices of physicians trained in chest diseases;" they must be supervised with utmost care. Only a certain proportion of minimal cases break down. Those with early evidence of progressive disease must be hospitalized. "It is wasteful to hospitalize all minimal cases when hospital facilities are grossly inadequate" and when "prolonged follow-up studies have demonstrated that only a limited number really needed sanatorium care."—"We must think of the community first and of the individual next. Available beds should be used principally for the spreaders of tuberculosis whose lesions can be arrested, and for minimal cases with labora-

tory evidence of active disease." A limited number of minimal cases may be hospitalized when the question of activity is still in doubt. "It is becoming more and more widely recognized that a tuberculous patient is not only an individual in a community but also a carrier of the disease in that community. We must choose carefully in terms of social welfare if limited resources are to be utilized and tuberculosis eventually eradicated."—*Economy of Bed Usage in Tuberculosis*, H. E. Hilleboe, *Pub. Health Rep.*, February, 1947, 62: 185.—(O. Pinner)

Case-finding.—A Board of Roentgenology consisting of five members was appointed by the Veterans Administration to investigate the relative diagnostic efficiency of the different roentgenographic and photofluorographic methods used in tuberculosis case-finding. The entire population of two Veterans Administration institutions were surveyed. A 35 mm. photofluorogram, a 4 by 10 inch stereo-photofluorogram, a roentgenogram on a 14 by 17 inch paper negative and a conventional 14 by 17 inch celluloid film were taken within a few minutes of one another of 1,256 persons. The films were interpreted independently by the five readers. The subjective errors were of two main types: (1) inter-individual variation, the failure of an individual reader to be consistent with other readers in interpreting the same set of films; (2) intraindividual variation, the failure of a reader to be consistent with himself in two independent interpretations of the same set of films. It is recommended that in mass surveys all films be read independently by at least two interpreters. The results of the analysis justify the conclusion that, except for a slight disadvantage to the miniature techniques resulting from overreading, not one of the methods is superior to any of the other methods.—*Tuberculosis Case Finding, a Comparison of the Effectiveness of Various Roentgenographic and Photofluorographic Methods*, C. C. Birkelo, W. E. Chamberlain, P. E. Phelps, P. E. Schools, D. Zacks & J. Yerushalmy, *J. A. M. A.*, February 8, 1947, 133: 359.—(H. Abeles)

Colleges and Control Programs.—The first Committee on Tuberculosis of the American Student Health Association was appointed in 1931. At that time no routine case-finding program existed, and diagnosis was on a symptomatic and delayed basis. Tremendous strides have been made in the past fifteen years, though all colleges do not participate. The tuberculin test is an essential part. A positive reaction demonstrates infection. An average of only 18.6 per cent of students reacted on admission to colleges in 1942-43. The incidence has been decreasing in the past fifteen years, to as low as 10 per cent in several schools in 1945. About 20 per cent of reactors show a primary lesion (calcification) by X-ray. (Calcifications may be due to nontuberculous causes in certain areas of the country.) Tuberculin reactors with primary infection, but without lesions on X-ray examination need close observation (50 per cent of the reactors, it is claimed, later develop disease). The X-ray film is not infallible as a screening method, as was demonstrated in examination of 18,000,000 candidates for the armed services. Far less than 50 per cent of those rejected with supposed tuberculosis had active disease, and 'normal' films of some of those who later developed tuberculosis were found to show lesions on reexamination. All Student Health Services should arrange for recurrent tuberculin tests, X-ray examination of reactors, complete clinical examination of all students, close observation of reactors with inactive lesions, care of those with active disease and examination of all contacts. Nursing and medical students have a special tuberculosis hazard because of their hospital contacts. They should not be allowed to care for tuberculous patients unless the most rigid contagious disease technique is used. The tuberculosis problem in schools can be solved better by use of established methods than by vaccines.—*Tuberculosis Control in Colleges and Universities*, J. A. Myers, *Journal-Lancet*, December, 1946, 66: 409.—(W. H. Oatway, Jr.)

Chest Survey in Dachau Concentration Camp.—Radiographic chest examinations were

made of patients admitted to one of the evacuation hospitals functioning as station hospitals in the Dachau Camp. Examinations were begun the day after arrival in the camp under overwhelming odds and with a typhus epidemic prevalent. Many of the patients first seen were in very poor physical condition and some were moribund. Among 2,267 patients examined, 626 had active pulmonary tuberculosis (27.54 per cent), 324 of whom (51.7 per cent) had bilateral disease. There were 365 cases with undiagnosed pneumonic densities and peribronchial infiltrations and 17 per cent of these had bilateral involvement. A large number of these, along with the 114 patients with pleural effusion, were doubtless tuberculous. Many persons were released, in spite of warnings, who were not examined or X-rayed. Tuberculosis was of a fulminating character, mostly in the moderately advanced or far advanced stages. The fibro-phthisical stage was rarely seen at autopsy. Malnutrition added to overcrowding undoubtedly contributed to the high incidence of tuberculosis. Pleural lesions were common. Fifty-seven patients had fractured ribs as the result of trauma. Enlarged hearts were observed in a considerable number of moderately and far advanced cases of tuberculosis and it was noted that the configuration of a great many hearts resembled the "beri-beri" type of heart so that avitaminosis may have played a large part as a causative factor. Cardiac displacement or distortion was seen in 30 patients due either to massive pleural effusion or fibrous band retraction. Numerous other chest conditions were also noted. The incidence of tuberculosis in Europe will be greatly increased in the next ten years due to the return of displaced persons from concentration camps who have undiagnosed active disease as well as a universally insufficient diet and overcrowding in large cities.—*A Radiographic Chest Survey of Patients from the Dachau Concentration Camp, A. D. Piatt, Radiology, September, 1946, 47: 284.*—(G. F. Mitchell)

Histogenesis of Tuberculosis.—The development of the granulation tissue typical for

tuberculosis, the epithelioid-giant cell tubercle, is always preceded by exudative changes. Between the cells of the tubercle, fibers gradually appear. Ultimately the entire focus is transformed into a nonspecific scar. This process is, in principle, the same in all organs. Caseation belongs to the exudative stage. A small caseated focus can be replaced by epithelioid-giant cell proliferation. A larger caseated focus can be surrounded by granulation tissue and then be encapsulated in fibrous tissue. It is wrong to speak of exudative and of productive tuberculosis; both processes are only phases in the development of the tuberculous disease. The prognosis of a tuberculous focus depends mainly on its size at the time of its origin. The prognosis depends, of course, also on the number of foci, on their localization and on the presence or absence of cavities.—*Histogenese der Tuberkulose und Einteilung der Lungentuberkulose, P. Huebschmann, Wien. klin. Wchnschr., August 9, 1946, 58: 450.*—(G. C. Leiner)

Development of Phthisis.—The current trend in French literature stresses the importance of exogenous reinfection. The author restates the arguments of the endogenists. It is admitted that calcified primary lung lesions are usually sterile and cannot be considered a potential source of endogenous propagation. However, virulent bacilli are said to be found in the hilar nodes in 10 to 20 per cent of cases, a fact which would be sufficient to explain the endogenous origin of pulmonary tuberculosis, since only a minority of persons with primary infection develop phthisis in later life. Moreover, the lymph nodes at the base of the neck, in particular at the venous angle, have been found infected in 81 per cent of cases. Other important reservoirs of bacilli are all extrapulmonary foci of the postprimary period, which are extremely frequent, although clinically mostly silent. From all these sources hematogenous propagation to the lungs takes place, producing the apical foci of Simon. A time interval of one to two years separates the primary period from the X-ray appearance of these lesions. Endobronchial

extension from carious areas within Simon foci leads to the development of the early infiltrate and to progressive phthisis.—*Sur l'origine de la phthisie*, A. Dufourt, *Rev. de la tuberc.*, 1946, 10: 15.—(V. Leites)

Pulmonary Faradization.—With the intention of influencing the nervous regulatory mechanisms of the lung and thus obtaining closure of cavities, pulmonary faradization was performed in 26 cases of pneumothorax with uncontrolled cavities. The electrode was introduced through a cannula into the pneumothorax space; 4 to 6 sessions were given at intervals of one to two weeks, each session consisting of four to six faradizations of the pulmonary surface in the neighborhood of the cavity. Among 7 cases of pneumothorax with adhesions there was disappearance of the cavity in 2 cases following this treatment; in 2 other cases the cavity diminished in size. No effect was obtained in the remaining 3 cases. Among 19 cases of pneumothorax without adhesions faradizations were performed early in 5 cases, all of which were successful; 15 cases received faradizations two to seven months after pneumonolysis. Cavity closure occurred in 13 cases. A common consequence of pulmonary faradization was the development of a transitory atelectasis, usually lasting four to six days.—*Traitement des cavernes résiduelles sous pneumothorax par faradization pulmonaire*, J. Braillon, *Rev. de la tuberc.*, 1946, 10: 252.—(V. Leites)

"Reflexotherapy" in Pulmonary Tuberculosis.—Intravenous injection of gomenol oil and neutral oil produced pulmonary reactions of a congestive nature similar to those provoked by intrapleural administration of various substances. In both cases perifocal reactions of a presumably nonspecific character occur, accompanied by fever. These nonspecific reactions can be exploited therapeutically inasmuch as they represent "useful" mechanisms—stimulation of tissue processes and "postcongestive sclerosis." Good results have been obtained in torpid forms of pulmonary tuberculosis. Great caution should be exerted in

the selection of cases. All cases with high allergy are to be excluded. Particular attention must be given to dosage and interval of injections in order to avoid exacerbations exceeding the desired result. The dangers inherent in this method are admitted.—*La réflexothérapie par voie intraveineuse dans la tuberculose pulmonaire*, P. Lefèvre & G. Weill, *Rev. de la tuberc.*, 1946, 10: 431.—(V. Leites)

Amphetamine in Pulmonary Tuberculosis.—The prevailing moods in tuberculosis patients are depression and increased anxiety. Anxiety over the outcome of various collapse measures often tends to vitiate the benefits of treatment. In an attempt to assist patients through the strain of thoracoplasty, 10 mg. of amphetamine sulphate were given orally daily. This produced slight euphoria, improvement in appetite and disappearance of minor complaints. In another group of patients, administration of the drug lessened the long strain of hospitalization. There was no insomnia or elevation of blood pressure.—*Amphetamine in Pulmonary Tuberculosis*, L. E. Houghton & F. L. Corrigan, *Lancet*, December 14, 1946, 2: 864.—(A. G. Cohen)

Sternal Puncture in Pulmonary Tuberculosis.—Comparative studies of blood and bone marrow were carried out in 35 cases of pulmonary tuberculosis. The first group of patients (18 cases) had far advanced cavity disease with marked constitutional involvement and high sedimentation rate. The second group (17 cases) had minimal or moderately advanced tuberculosis with positive sputum and low sedimentation rate. In both groups a close parallelism was found between the findings in the blood and in the bone marrow. The blood picture of patients with far advanced tuberculosis showed the usual hypochromic anemia, moderate leucocytosis with marked increase in the polynuclear cells up to 95 per cent and a corresponding decrease in the percentage of lymphocytes and monocytes. Bone marrow studies in this group showed impaired erythropoiesis with decrease in the number of erythroblasts and normoblasts, marked

increase of neutrophil myelocytes and polynuclears, and diminution of lymphocytic and monocytic elements. Blood and bone marrow examination in the second group of patients showed changes of the same nature as in the first group, but to a much lesser degree. A special study was made of the toxic granulations of leucocytes in the blood and in the marrow. The proportion of toxic granulations to normal granulations was established for each cell form. The group with far advanced disease revealed the presence of toxic granulations in over 50 per cent of polynuclear leucocytes.

The factor $\frac{\text{Toxic granulations}}{\text{Normal granulations}}$ varied between 1.2 and 1.9. In the bone marrow toxic granulations were found in the neutrophil polynuclears, myelocytes and promyelocytes, the incidence being highest in the youngest forms, where the factor was found to be 2.8-3.1. This factor was considerably lower in the second group of patients (0.04-0.35 for the polynuclears of the blood). In several cases of this group a factor higher than one for the cells of the bone marrow was found to indicate a tendency towards progression of disease.—*Myélogramme et granulations toxiques au cours de la tuberculose pulmonaire chronique*, L. Bethaux & A. Fabre, *Rev. de la tuberc.*, 1946, 10: 239.—(V. Leites)

Mass Radiography.—A group of 9,142 Royal Air Force personnel who had just returned to England after having been prisoners of war in Germany were X-rayed. This group did not include a certain number of cases unfit to travel and admitted directly to hospitals. In the group of nontuberculous abnormalities found there were 17 cases of aberrant pulmonic consolidation. This cleared on subsequent X-ray films (after termination of leave) or after a short hospital stay. The other nontuberculous abnormalities were not significant. There were 47 cases of active tuberculous infiltration (0.5 per cent). There were 64 cases of inactive pulmonary tuberculosis; 59 cases showing calcified nodules only; 27 with calcified hilar nodes and 51 showing both

calcified nodules and hilar nodes. Sixty-four per cent of the active infiltrations were in the 20 to 24 age group. Nineteen of the active cases were sputum-positive. After hospitalization and gastric washings were done, an additional 8 cases were found to be positive. Most of the men had been interned for a period ranging from one to four years. The higher incidence of disease found in this survey was attributed to factors associated with close living quarters and a lowered resistance—in the first instance due to mental stress and in the later stages actual malnutrition.—*Results of Mass Radiography of R.A.F. Ex-Prisoners-of-War from Germany*, A. G. Evans, *Brit. M. J.*, June 15, 1946, 1: 914.—(D. H. Cohen)

Inherent Efficiency of X-ray Methods.—The diagnostic efficiency of a particular radiographic method is limited by (a) "inherent errors" resulting from failure of certain types of films to record detail with sufficient clarity, and (b) "subjective error" due to poor judgment, lack of concentration or fatigue of the reader. The detail or clarity required of a particular type of film for the detection of pulmonary lesions varies widely according to the size, chemical composition and structure of the lesion. The ability of an X-ray film to record detail may be evaluated quantitatively by radiographing on it a test object having a pattern that can be carried from a fine to a coarse configuration. The ability of the eye to record detail varies with the eye and the film viewed. On the basis of these principles a simple method of studying the inherent error of all mass chest radiographic methods is described, and the experimental results are presented. It was found that fluoroscopy is not wholly satisfactory for detecting minimal tuberculous lesions, but that 35 mm., 70 mm., 4 by 5 inch celluloid and 14 by 17 inch sensitized paper are all inherently capable of detecting random samples of minimal, moderately advanced and far advanced lesions with a high degree of accuracy.—*The Inherent Efficiency of the X-ray Methods Used in the Detection of Tuberculosis*, R. H. Morgan, H. E.

Hilldale & I. Lewis, *Pub. Health Rep.*, February, 1947, 62: 201.—(O. Pinner)

Scanning of Chest.—There is a tendency to consider roentgen examinations of the chest infallible. A comparison of surgically removed lungs with their immediately preoperative X-rays reveals the fact that roentgen examination is frequently fallible. The flat plate by itself may record a coincidence of shadows which may assume a pathological pattern while, even stereoscopically, lesions may remain hidden or may masquerade as normal. The greatest reason for fallibility is lack of scale in X-ray emulsions and wave lengths of radiation which do not offer maximum tissue differentiation. In exposing for radiolucent areas, the more dense areas are greatly underexposed and, conversely, in exposing for radiopaque areas, thin areas are greatly overexposed, therefore compromise is used. Unfortunately, the two parts needing closest examination—the apex and the hilum—have the greatest tangles of black and white. The stereoscopic method proved most helpful in studying abnormalities on a thoracic surgery service. It has been found valuable, in order to obviate lag in memory in scanning stereos, to make comparison stereos on the same set of films, to be viewed simultaneously. Angulation between the two positions comprising such a comparison examination should be sufficient to make visible the mediastinal portions of the lung, but not so great as to make comparison difficult. Procedures are described for scanning of the apex, of the lungs as a whole, and for variations and combinations. This method may demonstrate disease not noted with other techniques.—*Roentgenographic Scanning of the Chest*, S. W. Atwell, *Dis. of Chest*, May-June, 1946, 12: 222.—(K. R. Boucot)

Phrenic Crush in Hemoptysis.—Two patients with severe hemorrhages from upper lobe cavities could not be treated with pneumothorax. Both were too sick for major surgery. Following phrenic crush the hemoptysis stopped in both cases.—*Die Phrenikusausschaltung als*

erweiterte Indikation bei Hämoptoe, E. Stangl, *Wien. klin. Wchnschr.*, September 27, 1946, 58: 568.—(G. C. Leiner)

Extrapleural Pneumothorax.—Extrapleural pneumothorax is the procedure of choice in early exudative cases with cavity formation and strong tendency to progress. It is also used successfully in bilateral cases when thoracoplasty should not be done because of reduced reserve, and in children and adolescents when thoracoplasty is avoided on account of postoperative scoliosis. Occasionally it is used successfully as an adjunct to unsuccessful intrapleural pneumothorax. When intrapleural adhesions cannot be successfully treated by pneumolysis, and reexpansion with thoracoplasty does not appear desirable, extrapleural pneumothorax with release of the adhesion bearing portion of the lung is performed. The pleura between the intrapleural and extrapleural spaces is divided and excised. High pressures are usually necessary to maintain the collapse, and because the mediastinum is usually fixed and the pleura thickened by previous intrapleural pneumothorax treatment, this can be done without difficulty. Two cases are cited which prove that extrapleural pneumothorax can also be successfully employed in the treatment of older, fibrotic cavity lesions. The operations were performed by Brunner who has accumulated 754 extrapleural pneumothoraces. He obtained sputum conversion in 66 per cent.—*Die extrapleurale Pneumolyse als zusätzlicher Eingriff bei partiellem und unwirksamen Pneumothorax*, J. E. Wolf, *Schweiz. med. Wchnschr.*, November 30, 1946, 76: 1245.—(H. Marcus)

Pneumoperitoneum and Phrenic Nerve Paralysis.—In 89 cases pneumoperitoneum had preceded, accompanied or was followed by a phrenic nerve paralysis. Lower lobe lesions gave the highest incidence of good results (50 per cent). Lesions which were centrally located within the lower lobes responded best. Disease in the upper lobes was favorably influenced in only a minority of cases.—*Valueur du pneumo-péritoine complémentaire de la para-*

lytic opératoire du diaphragme, F. Magnin, *Rcv. de la tuberc.*, 1946, 10: 407.—(V. Leites)

Schede Thoracoplasty.—The original incision for a Schede thoracoplasty was a posterior paravertebral hockey-stick incision. The author proposes an axillary approach. The advantages are: (1) ease of approach and closure of wound; (2) preservation of extra-thoracic musculature; and (3) avoidance of infection and postoperative complications of wound healing.—*Axillary Approach to Schede Thoracoplasty*, A. Lambert, *Surg., Gynec. & Obst.*, January, 1947, 84: 55.—(A. G. Cohen)

Arthritis and Tuberculosis in Childhood.—Although the occurrence of fleeting involvement of joints during the course of tuberculous infection is well recognized, chronic polyarthritis leaving definite residua has not been ascribed to a tuberculous etiology. Chronic polyarthritis with permanent deformity is rare in childhood. The reported cases are due to a variety of infectious agents, among which may be named congenital syphilis and hemolytic streptococci. The impression is gained that infection and predisposition are necessary for the production of chronic polyarthritis, and it is theoretically possible that at times the tubercle bacillus may be the infecting organism. Convincing cases of this nature have not been published. The author has observed 2 cases, in children of 7 and 10, respectively, in which it was evident that tuberculous infection and chronic deforming polyarthritis coexisted without any definite relationship. One child showed the development of a mitral lesion seven years after the onset of arthritis, and the other child developed rheumatic nodules four years after the first occurrence of arthritic symptoms. Both children developed permanent joint damage.—*Über die Beziehungen zwischen Tuberkulose und chronischer Polyarthritis des Kindes*, H. Wissler, *Schweiz. med. Wchnschr.*, November 30, 1946, 76: 1242.—(H. Marcus)

Breath-holding Test.—Reduction time, that is, the time required after occlusion of the cir-

culation for the reduction of hemoglobin to a constant level, depends upon the associated reactions basic to the supply of oxygen to the tissues. The response of the reduction time to breath-holding is a measure of the degree of homeostatic adjustment to a condition of stress. The score $\frac{\text{Resting reduction time}}{\text{minus reduction time after breathholding}} \times$

$\frac{\text{Resting reduction time}}{\text{Resting reduction time}}$
100 was determined for medical students on a normal, peace-time schedule and for students who were under the strain of an accelerated war-time schedule. It was 20.4 in the first and 14.7 in the second group. In subjects with a cold it was 10 or less. A score of 10 seemed to be the borderline between fitness and lack of fitness. The mean of 226 observations in hospital patients who had an active clinical condition was minus 13.5. In 177 Marines the mean was 29.9. Among these there were differences depending on the state of physical training. The mean for 92 subjects at a Naval Air Station was 29.1. During breath-holding the "peripheral circulatory reserve," the reserve blood present in the small vessels of the skin, is shifted to other areas of the body. The redistribution is the cause for the decrease in reduction time after breath-holding.—*The Change in Reduction Time of Blood after Breath-Holding as a Criterion of Physiological Fitness*, G. B. Ray, J. R. Johnson & Louise H. Ray, *Am. J. Physiol.*, December, 1946, 147: 636.—(G. C. Leiner)

Pulmonary Exchange and Artificial Respiration.—Experiments in man to determine the volume of air passing in and out of the lungs in artificial respiration are valueless unless the volunteer is unconscious, toneless and not breathing. Two volunteers were anesthetized profoundly and brought to respiratory arrest. Artificial respiration now became essential, since almost the only evidence of life was that the heart-beat continued. The various methods of artificial respiration were tried in turn and the pulmonary exchange recorded on a kymograph. A wide-base endotracheal tube was passed into the trachea and made other-

wise air-tight. Using Eve's rocking stretcher technique it was noted that a larger tidal exchange came about with the subject on his face than when on his back. Ventilation of the lungs increases with the angle through which the subject is rocked. Values ranging from 240 to 850 ml. tidal air were noted using this method. The Schafer method, as well as the Silvester method, were found inferior to the rocking stretcher method when the latter was done with the subject on his face and the angle was between 60 and 90 degrees. The "mouth-to-mouth" method and the artificial inflator method were found to be even better with tidal exchange values reaching 900 to 1,500 ml. In artificial respiration too much stress has been laid on unimportant outward details and not enough on absolute essentials, such as the maintenance of a clear airway. The authors further agree with the figures of artificial respiration carried out under deep surgical anesthesia and conclude that an apnoeic patient under deep anesthesia simulates the candidate for resuscitation by artificial respiration.—*Pulmonary Exchange during Artificial Respiration*, B. R. Macintosh & W. W. Mashin, *Brit. M. J.*, June 15, 1946, 1: 908.—(D. H. Cohen)

Experimental Pleural Effusion.—Fifty guinea pigs were inoculated intramediastinally with virulent tubercle bacilli of the human, bovine and avian type; 33 of the animals developed bilateral pleural effusions. The pathological changes consisted in the accumulation of leucocytes and histiocytes in the peri-esophageal and peri-tracheal tissue as well as in the lymph nodes within the first twenty-four hours. The involvement of lungs, liver and spleen was constant and occurred soon thereafter. The pulmonary changes were of an exudative nature. There was a marked congestion in the subpleural area. The pleura itself showed no definite histological changes; 50 per cent of the effusions were hemorrhagic. Lymphocytes predominated. Inoculation into guinea pigs revealed tubercle bacilli in all specimens of pleural fluid. Certain analogies are found between this type of experimental pleurisy and

sero-fibrinous pleurisy in man. The pathogenic principles of the latter are discussed and preference is given to the interpretation of pleurisy as a perifocal reaction in the neighborhood of a primary focus.—*Épanchements pleuraux expérimentaux chez le cobaye*, F. van Deinse, *Rev. de la tuberc.*, 1946, 10: 380.—(V. Leites)

Expulsion of Pathogenic Organisms.—Modern methods of observation have revealed that very large numbers of droplets are expelled during sneezing, coughing and speaking, and that most of these are small enough to remain air-borne as "droplet nuclei." These nuclei are the solid residues of these respiratory droplets which are small enough to evaporate completely before falling to the ground, after their formation they are capable of remaining air-borne for some minutes or for some hours, and of travelling long distances inside buildings. It has been found by those who have investigated the expulsion of pathogenic organisms by infected persons that aerial infection is much more limited than is suggested by the purely physical studies of droplet spray, and that the pathogenic organisms of the respiratory tract (for example, hemolytic streptococci and tubercle bacilli) are not expelled as rapidly or in as great numbers as the commensal organisms from a normal mouth or an indicator organism from an artificially infected mouth. It is suggested that infection is spread through the air mainly by infected dust particles liberated from clothing, bedding and room furnishings, after these have been soiled by the large infected droplets which fall out of the air within a few seconds of their emission. Recent evidence has shown that virulent diphtheria bacilli were present in large numbers in the floor dust of diphtheria wards, that these bacilli remained viable in the dust for some months, and that they were stirred up with the air by sweeping; viable pneumococci were demonstrated in room dust; and it was also shown that the influenza virus could remain viable in dust for some days or weeks. From other experiments it was shown that the production of air-borne infection with droplet

nuclei must depend mainly upon the presence of pathogenic organisms in the saliva of the anterior mouth. Faucial and nasal carriage may be of much greater importance with regard to the production of air infection with infected dust particles; pathogenic organisms may be expelled from the nose or from the throat in masses of secretion or in large droplets and so give rise to infected dust. The author's present investigation was concerned with three groups of infected persons: 87 persons with hemolytic streptococci in the throat, including 50 scarlet fever patients and 37 throat carriers; 50 faucial diphtheria patients with positive throat cultures and 20 patients with pulmonary tuberculosis, in whose sputum tubercle bacilli had been demonstrated. The mouth-spray droplets expelled by each person during a series of six voluntarily produced coughs were collected on a culture plate or microscopic slide (for tubercle bacilli) held about 3 inches in front of the mouth. Results revealed that 39 out of the 87 scarlet fever and throat carriers emitted droplets containing hemolytic streptococci; 1,109 infected droplets were expelled during 522 coughs. Hemolytic streptococci, usually in small numbers, were found in the anterior-mouth secretions of 13 out of the 87 patients. Droplets containing diphtheria bacilli were expelled by 10 out of the 50 patients with faucial diphtheria, 48 infected droplets during 300 coughs. Diphtheria bacilli, again in small numbers, were found in the anterior-mouth secretions of 12 out of the 50 patients. Droplets containing tubercle bacilli were expelled by 10 out of 20 patients with open pulmonary tuberculosis, out of 410 droplets collected during 120 coughs, 36 were found to contain tubercle bacilli. Before coughing, tubercle bacilli were found in the throat secretions of 15 out of the 20 patients, and in the anterior-mouth secretions of 10 out of the 20 patients.—*Expulsion of Pathogenic Organisms from the Respiratory Tract*, J. P. Duguid, *Brit. M. J.*, February 23, 1946, 1: 265.—(D. H. Cohen)

Decomposition of Oxygenated Water.—Oxygenated water, even in very low concentra-

tion, inhibits or kills a great many bacteria. Tubercle bacilli grown on Long's medium were shown to be stimulated when less than 2 parts in 100 of oxygenated water were added; more than 4 parts in 100 inhibits growth. One part of oxygenated water hardly reacts with pure Long's medium, whereas in the presence of tubercle bacilli, all other factors being equal, the decomposition of the water is rapid. The tubercle bacilli are responsible for this destruction, due primarily to their diastases. Attempts to stop the lowering of the potential by daily addition of a given quantity of oxygenated water and study of its influence on bacillary growth led to some interesting conclusions. By adding oxygenated water to Long's medium, freshly inoculated, during seven consecutive days at the rate of 1 part in 100 each day, the culture was seen to develop as regularly and as abundantly as the control. On the other hand, addition of 2 parts in 100 (total of 14 parts in 100) under the same conditions, proved to be bacteriostatic. Long's medium contaminated by skin and mouth organisms, to which 1 part in 100 of oxygenated water was added and inoculated subsequently with tubercle bacilli, showed bactericidal properties for all the bacteria of the associated flora, while favoring development of the tubercle bacilli. This difference in the resistance of common bacilli and tubercle bacilli against oxygenated water could be used profitably for isolating tubercle bacilli from specimens contaminated with secondary organisms.—*Sur la décomposition de l'eau oxygénée par le bacilles de Koch*, E. Andrejew, *Ann. Inst. Pasteur*, September-October, 1946, 72: 833.—(P. Q. Edwards)

Antigenic Substances.—Antituberculous immune sera contain certain antibodies reacting with an antigen in the protein fraction of the tubercle bacillus. This antigen associated with the protein is not the protein itself, it has been identified by Meyer as a polyosidic antigen. Research shows the existence in the tubercle bacillus of two specific polyosides differentiated by their serological and chemical characteristics. The simple

polyoside⁷ produces precipitation reactions at dilutions of over 1:1,000,000 with rabbit or horse tuberculosis antisera. It is soluble in 75 per cent alcohol and is precipitated by alcohol over 85 per cent. This substance also fixes complement in the presence of rabbit serum in dilution of 1:5,000,000, although a temperature of 4° C. is necessary. The other polyoside—polyoside complex—is precipitated with the proteins, particularly with the fraction which is precipitated by acetic acid at pH 4.0 and by half-saturated ammonium sulfate solution. Digestion by trypsin frees the polyoside from the protein. This substance causes precipitation with antibacillary horse and rabbit sera, as well as fixation of complement with these sera at a temperature well below incubation. The titre of these reactions is around 20 times lower than those of the simple polyoside. Sera exposed to the simple polyoside react later with the complex polyoside, whereas the reverse is not true, indicating that the complex polyoside contains two specific components: that of the simple polyoside and yet another of its own. Heating the complex polyoside for ten minutes at 100°C. in a N/5 solution of sodium carbonate destroys the specific constituent, thereby rendering it identical with the simple polyoside. The significance of these data in relation to other research is being discussed.—*Recherches sur deux polyosides de spécificité différente existant dans les filtrats de culture des bacilles tuberculeux*, W. Schaefer, *Ann. Inst. Pasteur*, September–October, 1946, 72: 783.—(P. Q. Edwards)

Fluorescence Microscopy.—An apparatus is described for the routine examination of pathological fluids for tubercle bacilli by the fluorescence method. This has proved entirely satisfactory. Examinations of 748 specimens of sputum, pleural fluid and gastric lavage were carried out by this method. The results were found to be as accurate, more sensitive and more rapid than with the Ziehl-Neelsen technique.—*Detection of Tubercle Bacilli by the Fluorescence Technique*, J. W.

Clegg & A. F. Foster-Carter, *Brit. J. Tuberc.*, July, 1946, 40: 98.—(A. G. Cohen)

Dyes in Media for Tubercle Bacilli.—The present paper has chiefly to do with determining which dyes are best for coloring nutrient media for contrast without materially interfering with the growth of graded plantings of tubercle bacilli. Three characteristic groups were noted in studying a large number of dyes. In the first group, the dye in most concentrations would color and be absorbed by the medium to an extent that no free dye was found in the liquid of condensation, and the inoculated bacilli would not be colored. In the second group the dye would color the medium, but in most concentrations, free dye was present in the liquid of condensation and the bacilli would also become colored or tinted by adsorption. In the third group, of which methylene blue was a classic example, the dye would color the medium by adsorption and usually the liquid of condensation would be clear and the tubercle bacilli would be colored a deeper tint than the medium. In studying the effect of dyes on the medium (Corper's egg-yolk), the dyes were added in sufficient concentration to color the medium without producing an appreciable retardation of growth from small plantings of tubercle bacilli. The dyes were grouped as azo, azine and triphenylmethane dyes. Some other dyes were not classified. The greatest contrast lies in the blues and blacks, since cultures of tubercle bacilli are usually buff or flesh color. Gentian violet is no longer used on account of its retarding effect on the bacilli. Malachite green is now used in many laboratories without the full realization that the dye is decolorized by growing bacilli and retards the growth of small plantings of bacilli. Congo red, which gives an orange tint in egg media, does not appreciably retard growth. In 1933 the authors suggested the use of trypan blue as it imparts a pleasing blue color to egg media without exerting an appreciable retarding effect upon the growth of bacilli. Dyed medium is not essential for trained technicians but, if contrast of colors is

desired, a blue or a black medium should be chosen. Black stains of standard composition have so far not been available and they may not be finally accepted.—*Contrast Coloring of Media by Dyes in Growing Tubercle Bacilli: Effect of Dyes on Growth of Tubercle Bacilli*, H. J. Corper & M. L. Cohen, *Am. J. Clin. Path.*, October, 1946, 16: 621.—(J. S. Woolley)

BCG Glucose Vaccine.—This is a review of a report by E. N. Leschinskaja (American Review of Soviet Medicine, February, 1946) of experiments by Leschinskaja and Vakengut of the BCG Laboratory, Central Institute of Experimental Medicine, Union of Soviet Socialist Republics. The purpose was to overcome the perishability of the BCG vaccine. It was found that BCG bacilli retain their viability better in a 50 per cent glucose solution than in other media. After a month of drying, the number of colonies obtained upon inoculation remains constant for several months. The dried vaccine may be stored at room temperature but the best method for storing is refrigeration. The glucose vaccine emulsifies readily. A standard sterile preparation was obtained; the growth of bacilli from this dry BCG after sixteen months of storage is approximately equal to that from a liquid vaccine preserved for two months. The dry glucose vaccine, as tested by animal vaccination after preservation for one and one half years, differs very little from fresh liquid vaccine.—*Review of the Immunization Value of the BCG Dry Glucose Vaccine*, (not signed), *Pub. Health Rep.*, February, 1947, 62: 211.—(O. Pinner)

BCG in Norway.—Because of the increased incidence of tuberculosis during the war, a campaign was initiated in 1943 to encourage immunizations with BCG. A total of about 42,000 people were immunized. Many vaccinated persons were not becoming tuberculin positive within two months. It was found that the war tuberculin was somewhat weaker than the pre-war material. This affected chiefly the Pirquet reaction; it had less influence on the number of reactors to the

Mantoux test with 1.0 mg. This fact did not adequately explain the small number of reactors. It was then shown that the Norwegian BCG vaccine had actually become weaker. Some increase in the number of positive reactors was obtained by increasing the dose. Late in 1945, a BCG strain was obtained from the Pasteur Institute in Paris. With this material, positive reactions were obtained in 96.8 per cent when 0.1 mg. was used. There were many local reactions. The dose was cut to 0.05 mg. which appears to be about the optimal dose. Other conditions which are considered necessary to justify mass immunizations with BCG are: (1) safety—there is no evidence that BCG has ever caused active tuberculosis; (2) lasting—tuberculin reactions were present after five to six years in 95 to 98 per cent of cases; (3) usefulness—in Oslo, immunization gave 75 to 90 per cent protection.—*Recent Experiences with BCG Vaccination in Norway*, G. Hertzberg, *Tubercle*, January, 1947, 28: 1.—(A. G. Cohen)

Delayed Tuberculin Reaction.—Two consecutive tuberculin tests were performed in 94 adult females at an interval of two weeks. The reactions were noted on the third and tenth day after each test. On the third day after the first test the proportion of non-reactors to reactors was 36 to 58, and on the tenth day 27 to 67, representing 10 per cent with delayed tuberculin reaction. At the time of the second tuberculin test 2 additional persons showed a reaction. Thus, the series which had started with 36 nonreactors terminated with only 16. An interpretation of these facts is attempted in analogy with the so-called "delayed dermatitis of sensitization."—*Existe-t-il une cuti-réaction retardée de sensibilisation a la tuberculine*, L. Marceron, *Rcv. de la tuberc.*, 1946, 10: 247.—(V. Leites)

Reactivation of Tuberculin Tests.—A case is reported of an active primary tuberculosis with generalization and terminal meningitis in the course of which local skin reactions occurred at the site of three Old Tuberculin

tests, performed four years, one year and six months previously. The first tuberculin reaction had been negative, the second doubtful and the third highly positive. Biopsy of the nodular skin reactions at the time of the active primary tuberculosis showed tuberculous tissue changes. Inoculation into guinea pigs was positive. It would seem that tissues previously impregnated with tuberculin, regardless of whether they had been the site of an allergic reaction, acquire a specific sensitivity to tuberculin and a capacity of fixing tubercle bacilli. In the light of such facts it seems that a tuberculous exacerbation at the site of an old focus is not necessarily to be attributed to an endogenous reactivation *in situ*. The hypothesis is advanced that old tuberculous foci can play a similar rôle of fixation of exogenous tubercle bacilli during superinfection as the old skin tests for endogenous tubercle bacilli in the presence of hematogenous dissemination in the above case.—*Éclosion simultanée de trois nodules tuberculeux sur d'anciennes cuti-réactions*, F. Bordet, *Rev. de la tuberc.*, 1946, 10: 438.—(V. Leites)

Pharyngeal Tuberculosis.—Primary tuberculosis in the pharynx is very rare; pharyngeal tuberculosis as a secondary manifestation of foci elsewhere in the body is uncommon. Three patients are presented, all young adults, in whom histories of repeated sore throats were given as the only symptom. In all 3 patients, cryptic tonsils were seen, with ulcerations either within the tonsil itself or on the pharyngeal wall behind the tonsillar pillars. Biopsies proved the tuberculous etiology in all cases, both histologically and bacteriologically. In spite of extensive clinical and X-ray studies in addition to repeated bacteriological examinations of sputum specimens, no extrapharyngeal tuberculosis was ever found.—*Trois cas de tuberculose pharyngée d'apparence primitive*, F. Piaget, J. de méd. de Lyon, October, 1946, 642: 701.—(P. Q. Edwards)

Laryngeal Tuberculosis.—A five-year study of laryngeal tuberculosis at the Blue Ridge

Sanatorium is presented. The period between 1-1-39 and 3-31-44 is contrasted with two previous five-year periods at the same institution. The percentage of laryngeal tuberculosis had decreased greatly. Marked dysphagia prevents swallowing without the use of an anesthetic spray. This is the group helped most by surgical treatment. There were 139 cases of laryngeal tuberculosis in 2,213 patients discharged from the sanatorium, an incidence of 6.2 per cent. This is in contrast to an incidence of 12.5 per cent in 1,090 patients discharged between 1923 and 1928 and 13.4 per cent in 1,139 patients discharged between 1933 and 1938. Treatment consisted of sprays and silence. In 78.3 per cent the laryngeal lesions were healed or improved at discharge and 76.6 per cent of the pulmonary lesions were arrested or improved. Treatment, in addition to spray and silence, consisted of galvanocautery and nerve block. The larynx improved or healed in 73 per cent. The chest lesions improved or healed in 55 per cent. All 27 cases of tuberculous laryngitis with advanced edema and ulceration had severe symptoms. Far advanced tuberculosis was present in 82 per cent on admission.—*Laryngeal Tuberculosis*, M. K. Humphries, Jr., *Dis. of Chest*, March-April, 1946, 12: 129.—(K. R. Boucot)

Bilateral Pleurisy.—Bilateral pleural effusion was observed in a 14-year-old boy, whose father had pulmonary tuberculosis. The clinical features of the case, as well as the physical signs and the X-ray findings pointed to a tuberculous pleurisy. The value of the physical signs is discussed in the differential diagnosis of tuberculous pleurisy. Although the guinea pig inoculation of the pleural fluid was negative, the tuberculous nature of the effusion was well supported by the presence of roentgenological signs of a simultaneous primary infection. The prognosis of a bilateral pleurisy in a young boy is serious, especially as far as future tuberculous manifestations are concerned. The indications for evacuation of the fluid are reviewed.—*Pleuresia serofibrinosa bilateral de origen bacilar*, N. Romans, *Prensa*

méd. argent., October, 1946, 33: 2157.—(L. Molnar)

Tuberculosis of Serous Membranes.—A review of 6,198 postmortem examinations of tuberculous patients from 1932 until 1945 showed an almost 100 per cent incidence of pleural involvement. Simple edema, sero-fibrinous effusion, miliary nodulation and the most different forms of sequelae were observed. Pleural adhesions were most frequent in the apical portions of the lung. Occasional observations of lungs recently re-expanded after pneumothorax have shown that adhesions may form very rapidly. Next to tuberculous pleurisy, peritoneal involvement was most frequently found, 261 cases (4 per cent), 91 in males and 170 in females. Aseites was present in 38 cases; fibro-adhesive forms in 100 cases; fibrocaceous lesions in 54 cases; miliary tuberculosis in 39 and peritonitis with a pearl-like appearance in 20 cases. In 77 autopsies meningitis was found (1.24 per cent): the great majority of these cases occurred in the age groups from 16 to 40 years, coinciding with the general age of tuberculous morbidity and mortality. Tuberculous meningitis was associated with pulmonary tuberculosis in 44 cases; with generalized miliary tuberculosis in 22 cases and with Pott's disease, genitourinary and osteoarticular tuberculosis and peritoneal involvement in 6, 9, 3 and 3 cases, respectively. Forty-four cases (0.71 per cent) of tuberculous pericarditis were observed, 31 in males and 13 in females. Involvement of the pericardium was noted more often in the middle-aged and in the more advanced age groups. Fibro-adhesive pericarditis was found in 32 cases; caseous, fibrinous and purulent forms were found in 6, 4 and 2 cases, respectively. Simultaneous involvement of pleura, pericardium and peritoneum occurred in 4 cases. Pericarditis was associated in one case for each with meningitis, pleurisy and peritonitis. —*Tuberculosis de las serosas*, E. Calderon & P. Renard, *Ap. respir. y tuberc.*, July-September, 1946, 11: 220.—(L. Molnar)

Pleurisy and Primary Complex.—The relationship between childhood-tuberculosis and pleurisy was investigated in 747 children with pulmonary tuberculosis between the ages of 2 and 12; 139 (18.6 per cent) had an early primary complex in an active stage. The total number of pleurisies was 93 (12.4 per cent). Early primary infection was accompanied by pleurisy in 24 per cent of cases. Pleurisy developed in most cases (75.5 per cent) while the primary complex was in an infiltrative stage and in 26.5 per cent during regression of the primary lesion. In 5 cases pleurisy was preceded by erythema nodosum. In 4 cases pleurisy was the first manifestation of infection, and the primary complex became evident after absorption of the exudate. In 9 cases primary complex and pleurisy appeared simultaneously. In 21 cases pleurisy developed during the months following the appearance of the primary complex. Primary tuberculosis uncomplicated by pleurisy showed an unfavorable course with generalizations in 14.3 per cent of cases, and death by meningitis in 3.8 per cent of cases, whereas primary tuberculosis associated with pleurisy showed an unfavorable course with generalizations in 38.2 per cent of cases and terminal meningitis in 11.8 per cent. Pleurisy was found less often in the postprimary than in the primary period and was of a milder type. Thus, the incidence of pleurisy in hilar adenopathy was 13.5 per cent, in pulmonary tuberculosis of the hematogenous disseminated type in 7.3 per cent, and in infiltrative forms in 4.4 per cent. The numerous cases of reinfection tuberculosis under observation (chronic fibrocavernous forms, caseous-pneumonic forms, etc.) were not associated with pleurisy. So-called idiopathic pleurisy was seen in only 18 cases.—*Pleurisy and Primary Complex in Children*, A. I. Odiova, *Probl. tuberk.*, (Russian), 1946, No. 3, 50.—(V. Leites)

Tuberculous Pericarditis and Miliary Tuberculosis.—A case of tuberculous epididymitis was followed several months later by acute pericarditis with effusion, a month later by miliary tuberculosis in subacute and later in

acute form, leading to death at the end of the third week.—*Péricarditis tuberculose et granulie*, G. Gregoire, M. Caron & J. E. Labrecque, *Laval méd.*, December, 1946, 11: 1003.—(E. Bogen)

Tuberculous Adenitis and Ocular Lesions.—A Bantu woman, aged 25, was admitted to the hospital complaining of blindness for two years and swellings in her neck for twenty-one months. Both eyes showed extensive plastic iritis with oclusio pupillae; these lesions were regarded as tuberculous. A number of discrete rubbery lymph nodes could be felt on both sides of the neck and in the submaxillary and submental regions. Radiological examination of the thorax was normal. A tuberculin intracutaneous test was strongly positive. Biopsy of one of the lymph nodes showed chronic fibroid tuberculosis; guinea pig inoculation of the material resulted in extensive tuberculosis. In cases of ocular tuberculosis, it is rare to detect a focus elsewhere in the body.—*A Case of Tuberculous Adenitis with Associated Ocular Lesions in a Bantu Woman*, P. W. Fleming, *Clin. Proc., Cape Town Post-Grad. Med. A.*, August, 1946, 5: 241.—(A. G. Cohen)

Intestinal Tuberculosis.—Primary intestinal tuberculosis is rare; it usually develops in a tumor-like form and is due to ingestion of raw milk of tuberculous cows. The ulcerative form of intestinal tuberculosis is not an exclusive attribute of far advanced pulmonary tuberculosis, it may be demonstrated also in a certain number of minimal and moderately advanced cases. While its prognosis is always serious, it is not as hopeless as it was thought to be. Vague gastrointestinal complaints, inconstant abdominal pain, often related to the right lower quadrant or to the periumbilical area, and diarrhea in patients with pulmonary tuberculosis are suggestive symptoms of intestinal tuberculosis. The diarrhea is almost always of the putrefactive and rarely of the fermentative type. Hemorrhage is rare; secondary anemia is frequent. Intestinal tuberculosis may sometimes simu-

late attacks of acute appendicitis or peptic ulcer. Its first physical sign is often a palpable ileocecal tumor. Roentgenological examination is the most important diagnostic procedure. Dilatation and segmentation of the small intestine are indirect signs of intestinal tuberculosis. Stasis in the ileum after seven to eight hours, and gas in this area are important signs; so is the sign of Stierlin, that is, a filling defect between two normally filled tracts. Proper management of the pulmonary tuberculosis is the first requirement in the treatment of intestinal involvement. Bland diet of high caloric value and of low residue is recommended; suitable amounts of vitamins and minerals should be administered. Calcium gluconate intravenously proves to be effective in combating abdominal pain and diarrhea. Sometimes opium derivatives are indicated. Artificial heliotherapy in increasing doses is of great help. Pneumoperitoneum is too little known in its effects on intestinal tuberculosis. Ulcerative intestinal tuberculosis is not treated by surgery, while the tumor-like form may be removed surgically.—*Tuberculosis intestinal*, A. R., *Prensa méd. argent.*, November, 1946, 33: 2238.—(L. Molnar)

Tuberculous Arthritis.—Taken singly, the individual roentgen signs of the arthritis are not pathognomonic. But taken together and in sequence, they give sufficiently reliable evidence for an accurate diagnosis. Tuberculosis of a joint is a metastatic process and may be in the synovial membrane or the bone contiguous to it. Early diagnosis is usually precluded by the insidious onset, and X-ray diagnosis lags behind clinical diagnosis. The life history of an active tuberculous arthritis is as follows: Cortical erosion osteoporosis, loss of joint space, invasion of underlying cancellous bone, involvement of the opposing surface of the joint, absence of reactive changes, formation of sequestra, accumulation of debris, rupture of the joint capsule and tracking of the fluid and debris with cold abscess formation and luxation of the joint. Some of these signs appear con-

currently and increase in intensity with the increasing severity of the process of the joint disease. No part of the joint is immune to tuberculous infection and if unchecked will ravage every portion of it. There is some variation in children as compared to adults.—*Tuberculous Arthritis of the Shoulder*, M. R. Camiel, *Radiology*, June, 1946, 46: 569.—(G. F. Mitchell)

Prostatectomy in Tuberculous Patient.—A series of 50 cases with fibroadenomatous prostates, removed by transurethral resection, is reported. Accurate diagnosis is essential, since 13.3 per cent of 748 cases coming to autopsy at Sea View Hospital had tuberculosis of the prostate. The two-stage suprapubic resection is considered best in nontuberculous patients in fairly good condition. The results following transurethral resection on debilitated tuberculous patients were much better than those in a previous series of suprapubic operations. This may be due to the shorter postoperative course which follows the former method, and the absence of an abdominal incision. The patients were carefully prepared; a low spinal anesthesia was used, and the operating time was limited to twenty or thirty minutes. There was no mortality, no hemorrhages, no ascending infection and no reactivation of pulmonary tuberculosis.—*Transurethral Resection for Hypertrophy of the Prostate in the Tuberculous Patient*, A. J. Greenberger & M. E. Greenberger, *Urol. & Cutan. Rev.*, October, 1946, 50: 590.—(W. H. Oatway, Jr.)

Pontine Tuberculoma.—In a 23-year-old female this syndrome of oculogyric paralysis with mild hemiplegia and marked hemianesthesia of the head on one side and of the body and limbs on the other, together with cerebellar symptoms, was recognized during life, as probably due to a pontine tuberculoma, and this was found at autopsy.—*Syndrome de Raymond et Cestan*, S. Caron, C. A. Martin, M. Samson & L. Patry, *Laval, méd.*, December, 1946, 11: 993.—(E. Bogen)

Sarcoidosis.—Sarcoidosis is rare in children. The reported cases in children are listed. A 6-year-old white Cuban boy is reported which is the first case observed at Children's Hospital of Habana. He had fever, polyarthritis and a symmetrical erythematous-macular eruption of the face and arms of three years' duration. The conjunctivae were hyperemic and a white pin-point spotty non-vesicular keratitis was present. The uveal tract was involved. Lymphadenopathy involved the groins, axillae, epitrochlear, and cervical nodes. Roentgenography of the lungs on 3-26-44 revealed bilateral miliary-like mottling. X-ray films of the phalanges on 7-4-44 were negative for evidence of sarcoid. On 10-16-44, X-ray films revealed a right pleural effusion with shift of the mediastinum to the left. On 11-16-44 atelectasis at the right base was present with an artificial pneumothorax on the right. The tracheobronchial nodes were enlarged. Bone marrow biopsy revealed giant cells similar to those found in sarcoidosis. Biopsies of the skin, subcutaneous tissues, muscle, lymph node and synovial membrane are reported. The child was discharged with a diagnosis of tuberculosis or Still's disease. Four months later he was readmitted with dyspnea, fever and weight loss. Biopsies revealed sarcoidosis. Since the paper has been submitted for publication, Pott's disease of the dorsal spine with death due to tuberculous meningitis has occurred. No autopsy was permitted.—*Sarcoidosis (Besnier - Boeck - Schaumann's Disease): Report of a Case in a Child Simulating Still's Disease*, A. Castellanos & E. Galan, *Am. J. Dis. Child.*, May, 1946, 71: 513.—(K. R. Boucot)

Uveoparotid Fever.—A 55-year-old workman had "influenza" and noticed a swelling below and in front of his ears; five weeks later fever and chills developed and on hospitalization swelling of both parotid glands was found. No eye symptoms were noted, except for an old cataract. During the following weeks the fever continued and pain in the eyes and deterioration of sight occurred.

Patient did not react to 1 mg. tuberculin and X-ray examination of lungs did not show evidence of sarcoidosis. There was bilateral chronic uveitis with corneal precipitate, somewhat turbid, aqueous, wide-spread posterior synechiae and striate keratitis of the left eye; there were no nodules on the iris. While this condition improved, myocardial failure set in. A few weeks later pleuritis developed; the X-ray film showed veil-like and stringy shadows of a bronchopneumonic appearance, but no signs of sarcoidosis. Patient died a month later from pulmonary infarct with suppurative pleuritis. Autopsy showed microscopical changes in the parotid glands and eyes and in the majority of internal organs, typical of sarcoidosis. There were generally noncaseating tubercles with large epithelioid cells and Langhans giant cells, surrounded by a thin layer of lymphocytes. Caseating necrosis in the centre of the tubercles was exceptional. Autopsied cases of uveoparotid fever are few. This case seems the only one in which, in addition to numerous organs, both eyes and several salivary glands were examined histologically. It is, therefore, the best possible substantiation for the modern concept that uveoparotid fever is a special manifestation of sarcoidosis. In this case very few acid-fast rods were demonstrated in a cervical and a hilar lymph node. Guinea pig inoculations from caseated lymph nodes were positive, but cultures from involved organs of these guinea pigs were negative.—*A Case of Uveo-Parotid Fever (Heerford) with Autopsy Findings, K. O. Granström, E. Gripwall, C. E. Kristoffersson & A. G. H. Lindgren, Acta med. Scandinav., 1946, 126: 307.*—(O. Pinner)

Bronchopulmonary Abnormalities.—Abnormalities of lobation: (1) Additional fissures: This is the most frequent type of abnormality. The cardiac lobe is formed by a fissure between the cardiac segment of the right lower lobe and the rest of the lobe. The dorsal lobe is formed by a fissure which partly separates the dorsal segment of the lower lobe from the remainder. The lungs

are otherwise normal. (2) Deficient fissures: Fissures are often incomplete or absent. (3) Fissure due to displaced structures: a) partial splitting of the right upper lobe by an abnormally placed azygos vein; b) sequestration of lung due to an abnormal artery. An anomalous artery associated with functional isolation of the part of the lung which it supplies. The bronchi in these sequestered areas are often dilated and cystic and do not communicate with the rest of the bronchial tree. Abnormalities of the bronchi: (1) Supernumerary bronchi: These are comparatively rare. Normal bronchi are present and additional branches arise directly from the trachea. (2) Displaced bronchi: These are relatively common. The most frequent example is upward displacement of the apical branch of the eparterial bronchus. It varies in degree from partial splitting of the parent bronchus to a frankly displaced apical branch arising from the trachea. Other abnormalities also are recorded. (3) Congenital cystic disease: This subject is more properly dealt with in separate treatises. Abnormalities of lung parenchyma: (1) Accessory lungs: These isolated masses of lung tissue are sometimes found in the thorax or abdomen. They do not communicate with the bronchial tree. The blood supply is derived from neighboring vessels. Histologically, they consist of bronchial and alveolar elements resembling fetal lung tissue. They are more common on the left. They are associated with congenital absence or malformations of the left diaphragm. (2) Agenesis of the lung: These are rare. All or part of a lung may be absent. There are three types: a) true aplasia, in which there is only one bronchus; b) there is one functioning bronchus; from this a rudimentary bronchus arises which is only a small nubbing; c) the rudimentary bronchus leads to a fleshy structure without lobes. (3) Hypoplasia: There is great variation in the size of the bronchopulmonary segments.—*Broncho-Pulmonary Abnormalities, A. F. Foster-Carter, Brit. J. Tuberc., October, 1946, 40: 111.*—(A. G. Cohen)

Coccidioidomycosis.—Since inactive pulmonary residues coccidioidomycosis may persist for months or years in apparently healthy persons, the recognition and interpretation of such lesions is of the utmost importance. Seventy-seven hospitalized cases and 200 out-patients are included in this report. Several clinical types of coccidioidomycosis are recognized. These include (1) the initial, or primary respiratory infection, which may or may not be asymptomatic, (2) an acute self-limited respiratory infection, manifested chiefly as a bronchitis, pleuritis or pneumonitis, (3) a respiratory infection accompanied by allergic phenomena, such as erythema nodosum, (4) apparently benign persistent (residual) pulmonary lesions often with cavitation or nodular formation, usually unaccompanied by constitutional symptoms or signs and (5) primary infection becoming progressive with wide-spread lymphatic and hematogenous dissemination. In the latter type, which occurs in the first few weeks or months of the infection, the lungs, meninges, skin, bone and tracheobronchial, supraclavicular and cervical lymph nodes may be involved. The most common type of the disease is the acute self-limited respiratory infection often clinically indistinguishable from the more prevalent nonspecific respiratory infections or atypical pneumonia. Fever is present in the majority of patients sometime during their illness and lasts about one week, but a considerable number may be afebrile throughout the entire period of observation. Nonproductive cough is present in less than half of the patients. Cutaneous manifestations differ in character with the stage of the disease. In about 18 per cent of the cases reported, erythema nodosum, less well defined erythematous eruptions simulating erythema multiforme or generalized irregular papular erythematous lesions involving the entire trunk are present. Granulomatous lesions, verrucous or papillary in character, or single or multiple cold abscesses and indolent sinuses may occur in disseminated cases. Painful arthritis, sometimes with slight swelling, is reported in approxi-

mately one-third of the cases. Most patients look and feel better than their clinical and roentgenological findings would indicate, and this is also true of the disseminated type. Except for cultural and inoculation tests, laboratory studies offer little of specific value in the diagnosis. Some findings are of value as an index of activity. The leucocyte count is usually elevated. An eosinophilia of over 10 per cent occurred in 23.3 per cent of the cases reported. The increased sedimentation rate is the most useful single index of activity. The disease may give a false positive serological test for syphilis. Roentgenographically, in the early phases, coccidioidomycosis may simulate various types of acute pneumonic lesions and later may be suggestive of lymphoma, malignant metastases and primary malignant lesions. Skeletal lesions in the disseminated type may resemble various neoplastic lesions, nontuberculous osteomyelitis and periostitis and other destructive bony and cartilaginous lesions. The X-ray findings follow five general patterns. In primary coccidioidomycosis the X-ray findings are limited to the chest, vary considerably in appearance but consist chiefly of pneumonitis. Adenitis cavitation, nodules and pleural effusion may also be found. The pneumonitis may consist of only a minimal increase in soft tissue markings in one hilar area which is easily missed, there may also be a perihilar or subpleural pneumonic infiltration. Consolidation of a lobe is rare, resolution may be complete in one to four weeks. Hilar and mediastinal adenopathy may disappear completely. Cavitation is generally thin-walled, irregular in contour, and usually is not seen in the upper lobes. Closure, probably a result of the predominance of fibrosis and bronchial occlusion, usually is permanent. Nodule formation corresponding to previous areas of pneumonitis, may be noted in serial films. Cavities are usually small, thick walled and round, and occur frequently in the lower lobes and right middle lobe. A history of exposure to coccidioidomycosis and a positive skin test may be of help in the diagnosis of patients showing nonexcavating nodules.

About 0.5 per cent of patients eventually develop progressive or disseminating type of infection. The greatest proportion of these occur in Negroes. In disseminated disease thoracic lesions may be chiefly hilar and mediastinal adenitis or pleuritis. Miliary distribution may occur, simulating miliary tuberculosis. Skeletal involvement is apt to be multiple, and to be associated with multiple joint lesions. The spine, pelvis, hands and lower extremities are the most common sites. Meningitis frequently occurs in disseminated disease. The diagnosis cannot be made by a positive skin test unconfirmed by cultural or serological tests. Yet failure to reach a correct diagnosis, especially when tuberculosis or malignancy is considered, may be disastrous. An absolute diagnosis requires: (1) observation of coccidioidomycetes in tissue sections, sputum, pus or pleural or spinal fluid, (2) recovery of the mycelial form on Sabouraud's media, and (3) demonstration of the spherules in inoculated animals. Gastric washing or bronchoscopy may afford material for examination. For practical purposes a diagnosis in the acute phase can be made with reasonable certainty if there is (1) a history of recent residence in an endemic area, (2) an acute respiratory infection with or without cutaneous lesions, (3) a positive coccidioidin skin test, and (4) a positive coccidioidin serological test. The skin test may be negative early in the primary infection but will later become positive in nondisseminated cases. Of 11 cases negative on admission, 7 became positive two or three weeks later. In 3 disseminated cases the test remained negative throughout the period of observation. A positive test has the same diagnostic significance and limitations as the tuberculin test. Precipitin and complement fixation tests are of value in both diagnosis and prognosis. In mild infections, late quiescent or inactive phases the tests are usually negative. The titre of complement fixing antibodies parallels the severity of the infection and in certain ranges may indicate impending dissemination. In late inactive phases with residual pulmonary cavitation or nodular focalization, the serological tests

are negative, even when the fungus is found in the sputum. Five patients in the series had disseminated disease and 2 died. Because of the variation of clinical patterns these cases are reported in detail to illustrate the protean features of disseminated disease, the possibility of recovery in even the most critically ill and the fallacy of evaluating therapeutic measures in individual cases. Treatment is nonspecific, and consists of rest, general measures and symptomatic treatment. It should be continued until the infection has subsided clinically and the chest lesions are stationary or completely healed. Abscesses may be incised and drained if penicillin is used to prevent secondary infection. Some advocate active treatment of pulmonary cavities.—*Clinical and Roentgenologic Aspects of Coccidioidomycosis*, C. F. Suckert, J. W. Turner & J. B. Gillespie, *Am. J. M. Sc.*, December, 1946, 212: 652.—(G. F. Mitchell)

Coccidioidomycosis.—The characteristic roentgen features of 60 cases of primary pulmonary coccidioidomycosis are presented. These are classified as follows: nodular lesions, peribronchial infiltration, confluent consolidations, hilar lymphadenopathy, pleural involvement, cavity formation, bilateral nodular (local) dissemination. The pathological findings with roentgenological correlation are presented in 2 cases that came to autopsy.—*Roentgenological Manifestations of Primary Pulmonary Coccidioidomycosis*, M. Rakofsky & T. W. Knickerbocker, *Am. J. Roentgenol.*, August, 1946, 56: 141.—(J. E. Farber)

Pulmonary Acariasis.—In some cases of tropical eosinophilia mites (acarina) were found in the sputum; many of these patients had not lived in the tropics but had worked in dusty atmospheres. Two cases are reported, not originating in the tropics. In one, a mite was found in the sputum. Both responded excellently to arsenicals. So-called tropical eosinophilia is apparently pulmonary acariasis.—*Tropical Eosinophilia or Pulmonary Acariasis*, G. A. M. Hall, *Brit. J. Tuberc.*, October, 1946, 40: 124.—(A. G. Cohen)

TUBERCULOUS MENINGITIS IN CHILDREN^{1,2}

With Special Reference to Serous Meningitis

Part I. Tuberculous Meningitis

EDITH M. LINCOLN

The clinical picture of tuberculous meningitis is well known, the prognosis is dire; only a small number of recoveries have been reported. Hope rises with the discovery of each new drug which proves to be efficacious in killing or retarding the growth of the tubercle bacillus. In a recent trial of promizole in the treatment of tuberculous meningitis on the wards of the Children's Medical Service at Bellevue Hospital (1) there was failure to cure any case, although we were having very encouraging results in the treatment of miliary tuberculosis with the same drug.

Any new drug which proves valuable in the treatment of tuberculosis in animals will first be tried in human beings against forms of the disease which are known to have very high fatality rates, since in this way the efficacy of a drug can best be demonstrated. It is reasonable to assume that disease will respond to therapy more quickly if treated early. Hence it is of the greatest importance that an early diagnosis be made. With this in mind the clinical picture of tuberculous meningitis has been reviewed with special reference to the character and duration of the prodromal symptoms. Moreover, if we are to evaluate the effect of a drug in terms of anything less than complete recovery or death it is essential that we know as much as possible about the natural course of the disease to be treated.

It is the purpose of this paper to analyze a series of cases of tuberculous meningitis studied in the Chest Clinic of the Children's Medical Service of Bellevue Hospital, and, in the paper which follows, to attempt to differentiate from tuberculous meningitis a clinical picture which is not infrequent in tuberculous children, which we shall call serous tuberculous meningitis. In the evaluation of new drugs it is particularly important that this latter clinical picture should not be mistaken for tuberculous meningitis since the prognosis is not as serious.

PATHOGENESIS OF TUBERCULOUS MENINGITIS

Rich and McCordock (2) in 1933 questioned the widely held belief that tuberculous meningitis was due to a direct hematogenous seeding of the meninges. In a detailed study of the brains of 82 cases they found focal caseous lesions older than the meningitis in communication with the meninges in 77 cases. They demonstrated cases of meningitis arising from small caseous cortical tubercles and from caseous meningeal plaques. Other investigators disagree

¹ From the Chest Clinic of the Children's Medical Service, Bellevue Hospital, and the Department of Pediatrics, New York University, New York, New York.

² Aided by a grant from the National Tuberculosis Association.

with this concept of the pathogenesis of tuberculous meningitis. Ragins (3) was unable to find older caseous foci apparently responsible for the tuberculous meningitis in 32 out of 39 cases examined. Beres and Meltzer (4) found no evidence of tubercles in the brain substance in 50 per cent of 28 cases of tuberculous meningitis. Cortical tubercles which might have been responsible for the coexistent meningitis were demonstrated in only 6 cases. Kment (5) found tubercles in the choroid plexus in 60 per cent of 27 cases and concluded that tuberculous meningitis was frequently dependent on the formation of such tubercles. MacGregor and Green (6), following the technique of Rich and McCordock, were also able to find caseous foci which they regarded as the source of the meningitis in 74 of 88 cases. Crowe (7) has called attention to tuberculous otitis media as a local cause of tuberculous meningitis. Both Rich and McCordock, and MacGregor and Green emphasize the fact that, while miliary tuberculosis and tuberculous meningitis are frequently associated, the age of the miliary tubercles in the rest of the body may not correspond with the age of the meningitis. In some cases the visceral tubercles are definitely older than the meningitis, while in other cases very small fresh tubercles are found in the viscera of an individual with an older meningitis. Therefore, these authors conclude that tuberculous meningitis is caused by a direct extension of the infection from a local lesion rather than by a sudden infection of the meninges by the direct hematogenous route.

ANALYSIS OF CASES OF TUBERCULOUS MENINGITIS

A series of 167 unselected cases was used for analysis; 75 of them were children not previously known to be tuberculous who were admitted to the Children's Medical Service because they were ill. The other 92 cases occurred in children in whom a diagnosis of primary tuberculosis had already been established and in whom tuberculous meningitis developed while they were under observation or during later follow-up. Intervals between the first diagnosis of tuberculosis and the onset of symptoms or signs of meningitis varied from one month to eleven and one-half years. Sixty-six of the children from this second group of cases died on the Children's Tuberculosis Ward at Bellevue Hospital; an additional 23 succumbed to meningitis in other hospitals. Three cases died at home one to two weeks after the diagnosis of meningitis had been established in the hospital. We were fortunate in being able to obtain complete records of the 26 cases who did not die on our wards and in addition in many instances valuable observations of the attending physicians. In 64 of the 167 cases the diagnosis was confirmed by autopsy, and in an additional 45 cases by finding tubercle bacilli in the spinal fluid on direct examination, by culture or by inoculation into a guinea pig. In 58 cases the only objective facts we had to confirm the clinical picture were changes in the spinal fluid characteristic of tuberculous meningitis. The low or falling sugar was the single diagnostic point on which we placed most reliance. We considered a clear spinal fluid with a high protein, a low sugar, a low chloride content and a moderate pleocytosis practically confirmatory of the clinical diagnosis of tuberculous meningitis, especially if there was pellicle formation on standing.

Seasonal variations: Chart 1 shows the distribution of cases by calendar months and seasons. Our figures agree with many authors in confirming the greatest frequency of tuberculous meningitis in the spring.

Sex and race distribution: There were 85 males and 82 females in our series; 87 white children, 37 Negro, 36 Porto Rican, 2 Mexican, 2 Chinese and 3 Filipino

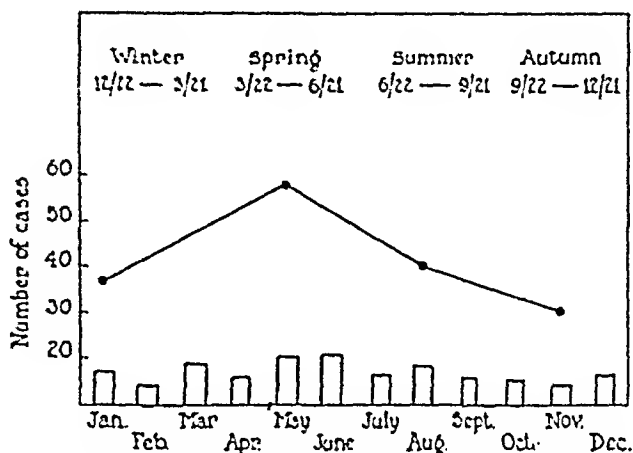


CHART 1. Showing distribution of cases of tuberculous meningitis by seasons and by calendar months.

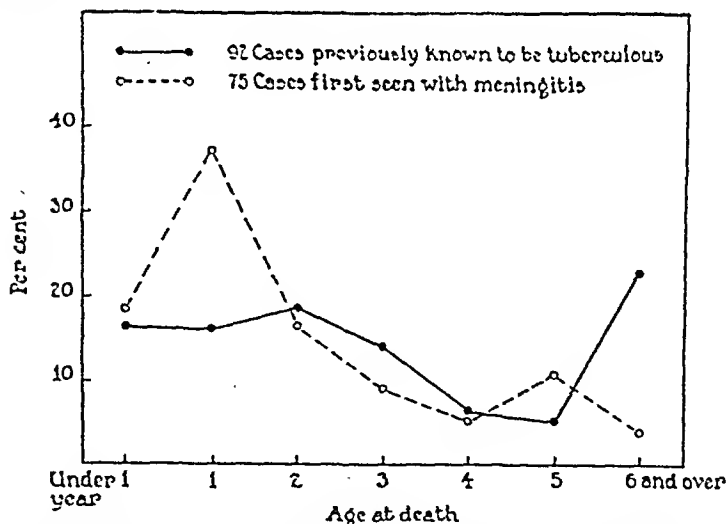


CHART 2. Age distribution of cases of tuberculous meningitis showing a much higher proportion of infants in the group not previously known to be tuberculous.

Age distribution: In the group of cases in which no previous diagnosis of tuberculosis had been made there is a strikingly large number of cases who died of meningitis between their first and second birthdays. In the group where treatment of the original tuberculous disease was attempted there is a more even distribution of cases up to the age of 5 and a much greater number of cases occurring after the age of 6 (chart 2).

Contact history: In New York City, the Department of Health attempts to find the source case of every child with tuberculous meningitis. In addition we urge the parents of every case of meningitis to be examined and to take their other children in for contact examination. Insufficient personnel for follow-up work and lack of coöperation from the families leave many source cases undiscovered so that we know the source case and the history of contact in only 97, or 57 per cent, of our 167 cases.

The source cases were as follows:

Father.....	27
Mother.....	27
Father and mother.....	2
Brother or sister.....	4
Aunt or uncle.....	16
Cousin.....	3
Grandparent.....	4
Friend.....	7
Boarder.....	4
Neighbor.....	3
Not found.....	70

167

There were two pairs of siblings in our series, one pair exposed to their mother who was found to be tuberculous when the first child developed meningitis. The mother refused to come into the hospital until the second child became ill. The other brother and sister were exposed to a boarder who was not removed until the second case developed. In 33 cases the exposure to a tuberculous patient continued until approximately the time of development of meningitis. In the other 64 cases the child had been separated from the source case for a month or more before the first symptoms of meningitis developed.

The absence of a tuberculous focus in the home was corroborated in a few cases by finding negative tuberculin tests in other children in the family. In other situations where no source case was discovered it was equally obvious that some member of the family group was the source case when 2 or more siblings of a patient with meningitis exhibited not only positive tuberculin tests but definite lesions of primary tuberculosis on X-ray examination.

Tuberculin tests: On the Children's Medical Service at Bellevue Hospital tuberculin tests are done on all children except those who are known to have had previous positive tests. Of the 75 cases who were admitted with signs or symptoms of meningitis, 5 children died before the test could be read; 60 children had positive tests at periods ranging from one to twenty-six days before death. At one time while tuberculin studies were in progress on the wards it was the routine procedure to give Mantoux tests with 0.01 and 0.1 mg. of tuberculin simultaneously in order to study the relation of the amount of tuberculin to the size of the reaction. In 7 of the cases admitted with meningitis the test with the smaller dose was entirely negative but there was a positive reaction to the

larger dose. In 10 cases no positive tuberculin test was ever obtained. Of these 10 children with negative tuberculin tests done from thirty-six hours to seventeen days before death, one was negative to 1.0 mg. of Old Tuberculin thirty-six hours before death. Two other cases gave negative tests to 0.1 mg. and 0.05 mg. on the tenth day before exitus. The other 7 were tested only with a Patch or a Mantoux test of 0.01 mg. Anergy to tuberculin was therefore relatively uncommon even in well developed cases of meningitis, since 85 per cent of the children whose tests were read had positive reactions and in an additional 10 per cent the final test was made with less than 1.0 mg. of tuberculin.

CLINICAL PICTURE OF TUBERCULOUS MENINGITIS

Of the 75 children who were not known to be tuberculous before admission 47, or 61 per cent, were diagnosed within twenty-four hours as having meningitis. Diagnoses were made chiefly by the appearance of the children and the neurological examination, in some cases aided by the history, and were confirmed by the findings in the spinal fluid. An additional 10 cases were at first thought to have other neurological conditions, most commonly poliomyeloencephalitis, brain tumor or brain injury; one apathetic drowsy infant was thought to be mentally subnormal. In the remaining cases the initial diagnosis was obscured by an acute infection such as tonsillitis in addition to the meningitis. In almost all cases not diagnosed on admission, the diagnosis was first suggested by positive tuberculin reactions and subsequent chest roentgenograms done as part of a routine examination, or by the results of lumbar tap because of convulsions. In one case the diagnosis was not made till autopsy.

Apparently, when tuberculous meningitis presents symptoms which alarm the family sufficiently to call for medical aid, the diagnosis is often obvious to the physician. On the other hand, our survey also suggests that the diagnosis of tuberculous meningitis, in the absence of the common neurological signs, may not be considered seriously until a tuberculin test, or more rarely a positive chest X-ray film, focuses attention on its possibility. The symptoms of which the patient or his parents complained are shown in chart 3 compared to the early symptoms noted by physician or nurse or in some cases by the parents in the group of 92 patients who developed symptoms of meningitis while under medical supervision. Forty-two of these children were under treatment for tuberculosis in Bellevue, an additional 16 were in other hospitals, 25 were under treatment or supervision at home and 9 were at home and were considered to have arrested tuberculosis.

Whether the child is at home or in a hospital under medical supervision, it is obvious that general symptoms such as vomiting, fever and apathy or drowsiness are the most common early complaints. Vomiting is not likely to be overlooked and appears about equally often in the parents' complaints and the nurses' notes. Drowsiness or apathy is noted slightly more often in the hospital. It might easily be overlooked by a mother whose child has a high fever and is vomiting. For some unexplained reason fever appeared more often as an early symptom in children admitted to the hospital with meningitis than

in those who developed meningitis under medical observation. The mothers also noted lack of appetite more frequently than did the nurses. On the other hand, irritability, a striking early symptom in the children who develop meningitis on the wards, may have seemed less important or less noticeable to the mother caring for a sick child at home or possibly the child at home in familiar surroundings is really less irritable than he would be in a hospital ward.

Some symptoms must be considered in relation to the age of the patient. For instance, headache which occurred in almost 20 per cent of the total cases was never noted under the age of 3 and only once at that age. In children 4 years old and over it occurred in 60 per cent. The greater frequency of headaches in the second group is explained by the greater number of older children. Convulsions occurred twice as often in the child at home who was not suspected of tuberculosis, as in the child who was known to have tuberculosis. Here again

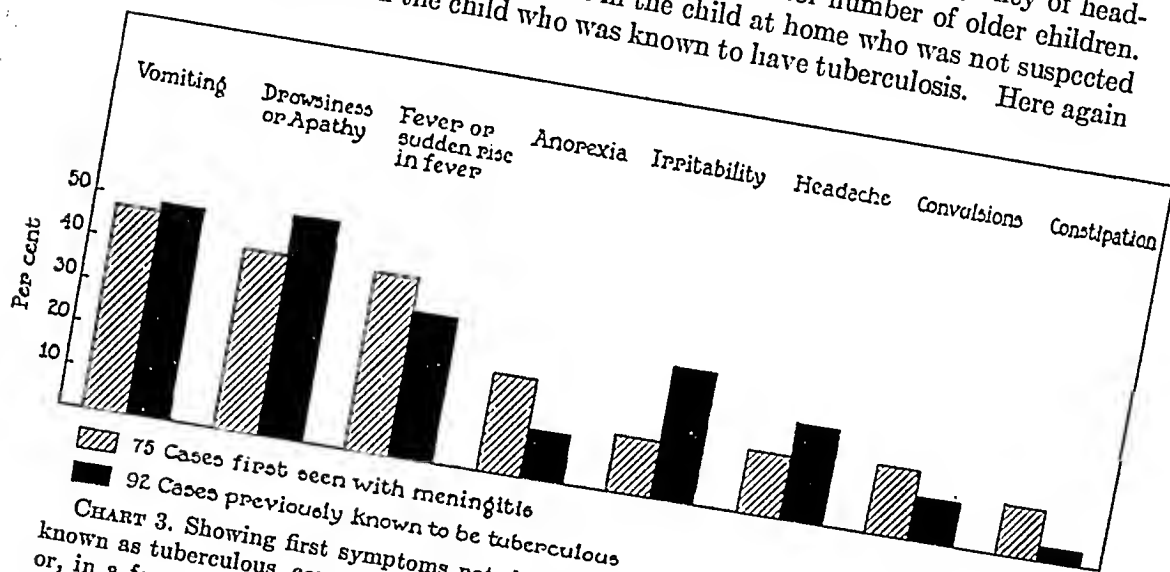


CHART 3. Showing first symptoms noted by patient or family in cases not previously known as tuberculous, compared with the earliest symptoms noted by physician or nurse or, in a few cases, by parents in cases which developed symptoms while under medical supervision.

age is a factor as the average age of children with convulsions was only 19 months, the oldest child being 5 years of age. However, age alone will not explain the marked difference in the two groups. Since tuberculous meningitis would be considered in any tuberculous child having general symptoms suspicious of the disease, it is possible that lumbar punctures were done earlier in the tuberculous group and this procedure may have played a part in preventing convulsions.

Duration of tuberculous meningitis: The duration of tuberculous meningitis from the onset of symptoms to death varied from one to sixty-three days; the average duration was nineteen and one-half days. Chart 4 shows that the duration of the disease calculated from the first symptoms noted by the parents approximates closely the time from first symptoms to death of patients under close medical supervision.

The usual mode of onset of tuberculous meningitis was insidious, the symptoms gradually or intermittently becoming more marked. During the first stage of gastro-intestinal symptoms, apathy and irritability, the neurological examination was entirely normal. However, a generalized convulsion was an early symptom noted in 16 children, or in 9.6 per cent of all our cases of tuberculous meningitis. An abrupt onset with a convulsion was more commonly seen in infants, occurring in 19.7 per cent of all cases under 2 years of age and never in children over 5 years old. During the second stage of increasing stupor, hyperactive deep reflexes, diminished abdominal reflexes, positive Kernig and Brudzinski signs, and ankle and patellar clonus sometimes appeared, usually transient at first. Evidence of involvement of the cranial nerves, most often strabismus, ptosis, nystagmus or facial paralysis occasionally appeared during this second stage. Fixed or unequal pupils, clonic spasms of one or more extremities and irregular respirations of the Biot type were also seen at this time

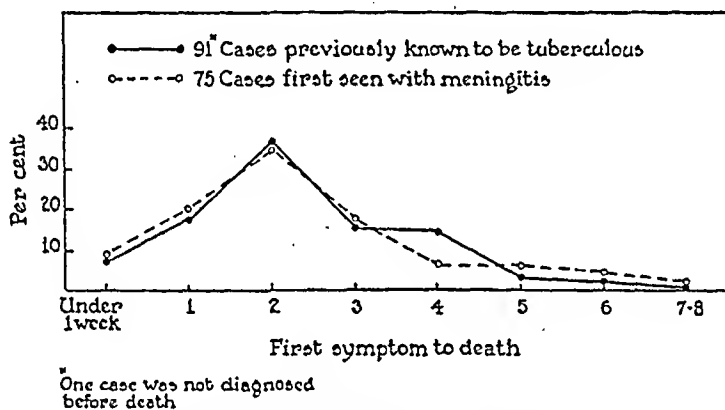


CHART 4. Duration of tuberculous meningitis showing marked similarity in curves although one was calculated from history given by parents and the other largely from observations of physicians and nurses.

but were seen more commonly in the final or comatose stage of the disease. Tubercles in the choroid were seen in 13 children, or in about 10 per cent of all patients in whom ophthalmoscopic examination was done. The finding of choroid tubercles was of no diagnostic help, since in 12 of the 13 cases there was an extensive miliary pulmonary tuberculosis and in the remaining child tuberculous meningitis was diagnosed a week before the choroid tubercle was first seen. "Stiff neck" in its early stage of resistance to flexion was often seen early but a rigid neck usually was not seen till later in the disease. The final stage of the disease was usually one of steadily increasing stupor but in rare cases there were intermittent periods of wakefulness with apparent return to normal cerebration. Terminal convulsions occurred in 6 per cent of all cases, practically always in fulminating cases. Some degree of nuchal inflexibility combined with positive Kernig and Brudzinski signs was almost invariably present in tuberculous meningitis. The relative duration of the three stages of tuberculous meningitis varied greatly. In the average case lasting about three weeks

they were often of almost equal length. In a fulminating case the general symptoms and neurological signs often became evident at the same time.

SPINAL FLUID

According to Levinson (8), the characteristic spinal fluid of tuberculous meningitis is a clear fluid with cells ranging in number from 10 to 350 per cmm., with predominating lymphocytes; with sugar below 50 mg. per cent and tending to decrease on successive taps; with chloride content which tends to be low. The fluid, on standing, usually develops a pellicle in which tubercle bacilli can be found in a large number of cases and theoretically in all cases. Records of 125 of our cases were analyzed and the majority of them did not vary greatly from this description. Details are shown in table 1.

TABLE 1
Spinal fluids of 125 cases of tuberculous meningitis

Cells per ccm.	NORMAL RANGE*	AVERAGE*	TUBERCULOUS MENINGITIS*	125 CASES	
	0-8	—	10-350		
Per cent lymphocytes	—	—	Over 50	350 or below	86.4%
Sugar mg. per cent	38-75	—	Under 50	351-500	7.2%
Protein mg. per cent	10-42	55	Over 50	501-1,000	4.0%
Chlorides mg. per cent	680-748	24	Low	Over 1,000	2.4%
		700		Over 50	87.2%
				Under 35	96.4%
				Over 24	99.4%
				Over 50	55.7%
				Under 680	86.7%†

* Levinson (8).

† Computed on 75 cases.

Occasionally one finds striking exceptions to the general rule. The low or falling sugar is the single most valuable diagnostic point in the spinal fluid, excluding the finding of tubercle bacilli. Nevertheless it is not an infallible sign since 4 children had a sugar of 77 mg. per cent nine days ante-mortem showed tubercle bacilli in the fluid as did another infant who had a spinal fluid sugar of 65 mg. per cent two days before death. The protein tended to rise as the disease progressed even if the initial reading was very high. A few very high readings were recorded. One infant had a spinal fluid protein of 24 mg. per cent five days antemortem which rose to 280 mg. per cent while the sugar fell from 22 to 11 mg. per cent. Two other children had sugars of 15 mg. per cent and a protein of 280 mg. per cent. A boy of 15, dying of meningitis eleven

and one half years after his primary tuberculosis, had a protein of 203 mg. per cent and a sugar of 4 mg. per cent. One child in whom meningitis was proved by autopsy had a count of 5 cells per cmm. two days before death.

OCCURRENCE OF HYDROCEPHALUS

It is well known that in tuberculous meningitis the free flow of cerebrospinal fluid from the ventricles may be impeded by the exudate. As a result it is not uncommon pathologically to find a slight degree of hydrocephalus. Indeed, Engel (9) stated that tuberculous meningitis always causes hydrocephalus. Clinically it is unusual to diagnose hydrocephalus except in cases of long duration. This diagnosis was made antemortem in one case whose first symptoms appeared two months before death. Her head increased markedly in circumference and hydrocephalus and tuberculous meningitis were proved by autopsy. In another case the diagnosis of hydrocephalus was made by an X-ray film of the skull showing very wide diastases of the sutures in a 2-year-old child whose first symptoms appeared thirty-two days before death. The relative infrequency of hydrocephalus at autopsy in patients with tuberculous meningitis who ran a short clinical course was striking. Of our total 167 cases, 105 had a duration of less than three weeks from initial symptom of meningitis to death. In this group there were 40 autopsies which included examination of the brain and hydrocephalus was noted 9 times, or in 22.5 per cent; with one exception there was only slight dilatation of the ventricles. Of the 62 cases which lasted three weeks or more after the first symptom of meningitis was noted, examination of the brain was done in 22 cases and hydrocephalus was found 14 times, or in 63.6 per cent. In this group there were 3 cases in which there was marked dilatation of the ventricles. The implication that hydrocephalus occurs more frequently in cases of longer duration seems obvious but it may be of importance in the treatment of tuberculous meningitis with drugs. A case with a short history would seem to offer a better chance of restitution to normal if the drug cured the meningitis. It is obvious that if we are to cure the disease before hydrocephalus develops the therapeutic agent used must act quickly.

IMPORTANCE OF EARLY DIAGNOSIS IN ATTEMPTED SPECIFIC THERAPY

Since the most common early symptoms of the disease are those often seen in children at the onset of minor illnesses, the greatest number of early diagnoses will be made in cases where the child is known to be tuberculous and the suspicion of meningitis is early aroused. The child who has a convulsion as the initial symptom will only be diagnosed promptly if a lumbar puncture is done, but unfortunately this is not the usual practice for a single convulsion, unless the child is in a hospital or is known to be tuberculous. The fulminating case or case of short duration will present the greatest difficulties in attempting treatment. The following group of cases are presented to illustrate the difficulty of early diagnosis of some forms of tuberculous meningitis.

Case Reports

The first case is an example of tuberculous meningitis with a very short clinical history.

Case I: L. K., a white male baby, 15-months-old, was admitted to the children's surgical ward 1/13/36 for circumcision. His mother and the physicians who examined him thought he was a well baby. The nurses' notes record that he took food normally. He was discharged twenty-four hours after circumcision under ether anesthesia, and his mother noted lethargy and lack of appetite on the same day, but thought it due to the operation. The next day there was a drooping of the right eyelid. The baby continued to refuse food, to sleep most of the time and to be constipated. He was admitted in coma to the Children's Medical Service 1/21/36, eight days after circumcision. The fontanelle was bulging; there was ptosis of the right lid. The pupils showed no reaction to light; early bilateral papilledema was present; deep reflexes in the upper extremities were absent and were just obtained in the lower extremities—more readily on the right side. A tentative diagnosis was made by the neurologists of a partial hemiplegia probably of embolic origin. Spinal fluid was under increased pressure, clear, showed 200 cells per cmm., 64 per cent lymphocytes, sugar 22 mg. per cent, protein 256 mg. per cent, chlorides 630 mg. per cent. He died within ten hours and an examination of the fluid removed by a post-mortem cisternal tap showed tubercle bacilli.

Another stumbling block to early diagnosis is the case without neurological signs. However, if a child is known to be tuberculous, an early diagnosis of meningitis may be made before neurological signs appear, as in the following case:

Case II: R. A., a Negro boy, 2-years-old, was under observation in the hospital for primary tuberculosis and in about two months developed hematogenous tuberculosis. Two weeks after this condition was first detected on X-ray examination he became suddenly very cranky and within four days was sleeping most of the time, showing marked irritability when aroused. Neurological examination continued entirely normal, but a spinal tap ture revealed a fluid characteristic of tuberculous meningitis, under increased pressure, with increased cells and low sugar content. It was not until one week after the spinal tap that he first developed a stiff neck, positive Kernig and Brudzinski signs. He became increasingly spastic with opisthotonus and athetosis and died thirty-nine days after irritability was first noted. The diagnosis of tuberculous meningitis was confirmed at autopsy.

The early recognition of tuberculous meningitis may be obscured by the presence of an acute incidental infection as in case III, especially if the neurological signs do not appear until late and the child was not previously known to have tuberculosis.

Case III: T. W., a white girl, 5-years-old, was admitted to the ward 3/31/37 because of sudden onset of fever, headache and drowsiness, associated with stomatitis. Tuberculin tests during a contact examination in December, 1936 had been negative. She was an apathetic child with temperature of 103°F., aphthous ulcers over the inner cheeks and tongue and heavily crusted lips. There had been a loss of 4 pounds in a week. Bilateral non-tender cervical adenitis was present. Neurological examination was entirely negative on admission and a diagnosis of stomatitis was made. Tuberculin test, repeated as part

of the routine examination, was positive on 4/13/37 and a chest roentgenogram revealed miliary tuberculosis. The neurological examination was still entirely negative, but, because of the X-ray findings and continuing drowsiness, a lumbar puncture was done. The fluid was clear, under markedly increased pressure; there were 42 cells per cmm., all lymphocytes; protein was 60 mg. per cent, sugar 20 mg. per cent. This child never developed any stiffness of the neck nor positive Kernig nor Brundzinski signs. During the last two days of life, the deep reflexes in the legs were absent, as were the abdominal reflexes. She developed nystagmus and irregular respirations of Biot type and there was a marked tache. Her temperature rose to 104°F. and she died 4/16/37, three days after the miliary tuberculosis was found on X-ray examination. In spite of the fact that tubercle bacilli were not found in the spinal fluid, I believe this could only have been a case of tuberculous meningitis. The spinal fluid is characteristic and the disease was associated with miliary tuberculosis in a child whose primary tuberculosis is obviously recent, since she was known to have negative tuberculin tests four months before death.

The diagnosis of tuberculous meningitis soon after the onset of symptoms is unlikely except in the group of children under treatment or observation for tuberculosis. Even in this group we shall have to train ourselves to think of the possibility of a meningitis whenever a child who has tuberculosis manifests any of the general symptoms associated with the onset of meningitis, such as irritability, apathy or vomiting. The following case illustrates the very gradual nature of the onset:

Case IV: J. R., a Negro male, 11-years-old, was on the ward of the Children's Medical Service from July, 1943 to July, 1945. He had a massive tuberculous pleurisy with effusion which became caseous and by November, 1944 showed extensive calcifications in the pleura and in axillary and mediastinal nodes. His disease was considered quiescent and he was to go home after graduation from the hospital school. On 6/6/45 his temperature which had been normal began to show daily rises to 101°F. A few days later he began to complain of headaches and frequent administrations of aspirin appear on the nurses' notes. He was a very bright boy and his teacher commented on inattention and unusual behavior in class. There was no change in his physical examination and he was sent in turn to the eye clinic, the dentist and the otolaryngology clinic, but no one could find a cause for his headaches. On 6/14/45 he vomited while riding in the elevator coming from clinic. On examination a few hours later there was a definite slight stiffness of his neck and he complained of pain on flexion of the neck. A lumbar puncture was ordered but was canceled that same evening when he was found playing merrily with the other boys in his room; the neurological examination was normal and remained so for four days. By 6/18/45 stiff neck had recurred, he looked miserable, was unable to retain even water; he said that the headache was "behind the eyes," but that it disappeared completely at times. A spinal fluid obtained at this time showed clear fluid, under increased pressure, containing 100 cells per cmm., all lymphocytes; protein 38 mg. per cent, sugar 38 mg. per cent, chlorides 706 mg. per cent. He lived for three and a half weeks after this fluid was obtained. For several days at a time neurological examination was entirely negative, then stiff neck recurred and transient ankle clonus was noted. Breathing was at times irregular, of Biot type; his mentality remained clear until death. A second spinal fluid on 6/22/45 showed 150 cells per cmm., sugar had fallen to 24 mg. per cent, and chlorides to 673 mg. per cent. A tap immediately after death on 7/12/45 showed a cell count of 2,160 per cmm., no sugar reaction and chlorides of 614 mg. per cent.

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In a case like this, with the possibility of specific therapy in mind, a lumbar puncture should be done within a day or two at most of the development of any unexplained symptom, such as headache. Vigilance in suspecting tuberculous meningitis, even if the primary tuberculous prodromal symptoms must be maintained, is apparently healed. This is illustrated by the following case:

Case V: E. M., a white male, had a primary tuberculosis of the left upper lobe at the age of 3 years. He was observed in the dispensary at regular intervals. X-ray films showed a progressive calcification of the primary focus and its regional nodes. On 2/11/43, when 15-years-old, he was seen in the dispensary in apparently excellent condition. There had been a weight gain of 10 pounds and complained of pain in his neck. Five days later he had a headache with fever and entered a hospital where his previous history of tuberculosis was unknown. His physical examination was entirely negative and he was given sulfonamides. During the following six days his temperature fluctuated from 100° to 103°F. daily; headache continued; neurological examination was entirely negative. On 3/1/43 he first developed a stiff neck and a lumbar puncture revealed a clear fluid with 28 cells per cmm.; sugar 4 mg. per cent and protein 253 mg. per cent, chlorides 667 mg. per cent. He speedily developed the clinical picture of tuberculous meningitis and died seventeen days later, the diagnosis being confirmed at autopsy.

FACTORS WHICH MAY PRECIPITATE TUBERCULOUS MENINGITIS

If Rich and McCordock's explanation of the pathogenesis of meningitis is accepted, an attempt should be made to discover what extraneous factors may cause a perifocal reaction around a previously established intracranial focus of tuberculosis.

In 5 of our cases a definite severe pertussis preceded the onset of tuberculous meningitis by five to twelve weeks. Sixteen of our cases, or 9.6 per cent, had measles within three months of the onset of meningitis. The rôle of these infections as predisposing factors to tuberculous meningitis has also been stressed by Herben and Asserson (10).

The action of trauma in the production of tuberculous complications of all kinds has been discussed frequently. A severe fall seemed more than coincidental in 5 of our cases. Two examples follow:

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Case VI: E. F., 2-years-old, fell down stairs 8/2/30 and landed on his head. He was admitted to the hospital for a possible fracture of the skull; the next day he was drowsy and two days later he vomited a few times. As X-ray films of his skull were normal, he was sent home, but he continued to vomit once or twice daily and was drowsier than usual. On 8/23/30 he was readmitted and a diagnosis of brain laceration was suggested by the visiting neurologist. Spinal fluid on 8/27/30 showed 26 lymphocytes per cmm. in a fluid under increased pressure; on 8/30/30 he developed a slightly stiff neck; on 9/3/30 he began to have frequent generalized convulsions and he died 9/5/30. Tubercle bacilli were recovered from his spinal fluid which contained 250 cells per cmm., 50 per cent lymphocytes, and had a sugar content of 25 mg. per cent.

Case VII: W. J., 5-years-old, had tuberculous pleurisy with effusion in January, 1938; in September, 1939 a diagnosis of tuberculous involvement of the eleventh and twelfth dorsal vertebrae was made and a spinal fusion was done soon thereafter. He was discharged from orthopedic care in September, 1941, apparently cured. On 10/12/42 he fell while skating but sustained no local injury. On 10/14/42 he began to complain of headache. He died ten days later of tuberculous meningitis; tubercle bacilli were found in the spinal fluid.

Possibly other forms of trauma may play a part in activating caseous foci of tuberculosis.

Case VIII: M. S., 7-years-old, had a primary tuberculosis of eighteen months' duration which was apparently diminishing according to X-ray appearance, when she was badly frightened by a fire which destroyed her home. We were all impressed by the mother's statement that the child seemed well before the fire, but within a few hours began to complain of a severe headache. This symptom continued in spite of the usual medication, and she was admitted to Bellevue Hospital two weeks after the fire, still complaining of constant headache. Neurological examination was negative, but two days after admission she became drowsy, then developed a stiff neck and died thirty-one days after the fire. There was postmortem evidence of tuberculous meningitis, a caseous primary pulmonary lesion and miliary tuberculosis of lungs, liver and spleen. It is certainly within the realm of possibility that the physical reaction to a shock may have activated a focus of tuberculosis.

The rôle of excessive exposure to sun in activating tuberculous foci has been discussed by Mayer (11). The probability that the factor of sunburn precipitated the meningitis in the following case cannot be disregarded.

Case IX: E. L., a white infant, developed a severe sunburn and two days later became drowsy and refused food. Four days later she began to vomit and was admitted to the hospital one week after the sunburn because of a convulsion. She died ten days after admission and, on autopsy, showed a primary pulmonary focus of tuberculosis with a cavity, very early miliary tuberculosis and tuberculous meningitis.

We know that a general reaction to a tuberculin test may precipitate a meningitis. One striking case has been reported before (12), but is repeated briefly:

Case X: D. C., a Negro girl, 9-years-old, had an extensive primary pulmonary tuberculosis in December, 1935. She did well on bed-rest and, in February, 1936, only the node component of the primary complex was still visible. On 2/27/36, after a physical examination which showed no abnormalities, a Mantoux test with 0.1 mg. was done, followed within twenty-four hours by a fever of 103°F., a severe headache and a marked local reaction to tuberculin. She was admitted to Bellevue Hospital on 2/28/36 and died of meningitis on 3/7/36. Here again the mother and the physician gave striking evidence that the child seemed well until an occurrence which might have been a factor in causing a perifocal reaction. In the mother's own words the Mantoux test seemed "to scatter the disease."

Surgical operations, particularly tonsillectomy and orthopedic procedures, have been stressed by various authors as predisposing factors to tuberculous meningitis. Ten children with tuberculosis of the bones underwent orthopedic

surgical procedures with no untoward effects, but 2 children who showed well calcified primary tuberculosis on X-ray films developed meningitis thirty-three days and two months after corrective orthopedic surgery. One of these cases is cited:

Case XI: R. B., a white male, 11-years-old, was operated on for tuberculosis of the left hip joint and femur in January, 1931. He remained in good condition, but on 8/9/31 a hip abduction under gas anesthesia was performed. The next day the boy had a severe headache which only subsided at the end of a week, and fever of 104°F. for one day, followed by a low grade temperature always under 101°F. He had no further symptoms until 10/8/31 when frontal headache recurred accompanied by projectile vomiting and followed in forty-eight hours by pain on flexion of neck. He died on 10/22/31. On post-mortem examination a calcifying caseous primary focus was found in the lung, miliary tuberculosis of the liver, kidney and spleen and a tuberculous meningitis.

Only one case in our series had a tonsillectomy which probably precipitated a meningitis.

Case XII: D. K., a white girl, 20-months-old, had a bilateral mastoidectomy for chronically discharging ears in December, 1932. She had been diagnosed tuberculous two months previously, having a positive tuberculin test and a large primary focus in the right lung. She made a good recovery from the first operation, but three months later a tonsillectomy was done although it was the opinion of the members of the Chest Clinic that it was inadvisable. She continued to have persistent low grade fever and, within a month, fine mottling appeared on X-ray films; she gradually developed the typical picture of a tuberculous meningitis and died two months after tonsillectomy. There was autopsy evidence of a calcifying caseous primary lesion with miliary tuberculosis and a tuberculous meningitis with an underlying tuberculoma in the left parietal lobe.

TIME INTERVAL BETWEEN PRIMARY TUBERCULOSIS AND MENINGITIS

In the groups of 92 cases where we knew the child before meningitis developed, we had an excellent opportunity to study the time relationship between the discovery of primary tuberculosis and the development of tuberculous meningitis. Forty cases occurred three months or less after the discovery of the primary lesion, and another 19 occurred within six months. Seventy-one of the 92, or 77.2 per cent, succumbed to meningitis less than a year after the diagnosis of tuberculosis was made. Details are shown in chart 5.

CLINICAL EVIDENCE OF AGE OF PRIMARY FOCUS IN CHILDREN WHO DIED OF MENINGITIS

Obviously if we could date the onset of primary tuberculosis in all cases, the time interval between onset of the disease and death from meningitis could be determined correctly.

Wallgren (13) cites 60 cases of meningitis of which 20 are from his own records in which the date of onset of primary tuberculosis was known. We have many patients in whom the time of onset seems definite, but unfortunately we do not have the corroborating evidence of a negative tuberculin test and negative

X-ray film previous to the supposed onset of tuberculosis. We can, however, cite 3 cases in which the date of onset of tuberculosis was known.

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Case XIII: I. F. had contact with her tuberculous mother. On 12/26/42, when she was 10-months-old, a Mantoux test with 0.01 mg. of tuberculin and chest X-ray examination were negative. Mantoux test repeated on 1/14/43 with 0.1 mg. tuberculin was positive. X-ray showed enlarged broncho-pulmonary nodes on the right side. By 1/22/43 she showed slight mottling in both lung fields which progressed to definite miliary tuberculosis. Irritability was first noted on 3/13/43 and she died on 3/26/43, less than three months after the onset of tuberculosis. Tubercle bacilli were demonstrated in the spinal fluid by guinea pig inoculation.

Case XIV: S. P. was examined as a contact case at the age of 2 months and at this time (3/5/31) he had a negative Mantoux test with 0.05 mg. of tuberculin. He was followed

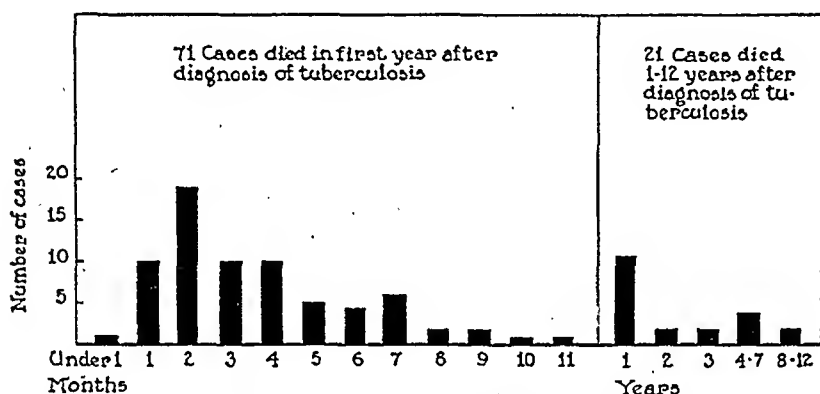


CHART 5. Showing time interval between first diagnosis of tuberculosis and death from meningitis; 43.5 per cent of the 92 cases died in three months or less after the first diagnosis of tuberculosis; 77.2 per cent died less than a year after the first diagnosis of tuberculosis.

in the dispensary until 10/1/31 when he suddenly developed fever without other symptoms and was admitted to Bellevue Hospital. Mantoux test was positive with 0.01 mg. of tuberculin. An X-ray film showed slight enlargement of the left root. Liver and spleen became moderately enlarged, the fever persisted for two weeks; then, the child went home symptom-free. No cause, other than tuberculosis, was found for the fever which was thought to date the onset of the disease. On 11/23/31 he began to be very drowsy and was readmitted to the hospital on 11/29/31. He died on 12/3/31 of tuberculous meningitis, two months after the onset of tuberculosis. On autopsy he had a fresh caseous lesion of the left lower lobe, miliary tuberculosis and tuberculous meningitis.

Case XV: G. B., 9-years-old, was admitted to a hospital on 3/10/31 with a three-day history of cold, fever and cough. X-ray examination showed a dense shadow over the right lower lung field. There were dullness and diminished breath sounds over this area but no râles. Mantoux test was negative even with 10 mg. of tuberculin. Within seven weeks her Mantoux test became positive and she developed a hematogenous pulmonary tuberculosis. Twenty-one weeks after the onset of tuberculosis she developed a headache

and a sudden elevation of temperature and died seventeen days later, showing on autopsy, in addition to tuberculous meningitis, three caseous primary foci in the right lower lobe, in 2 of which softening and cavitation were present.

The usual tendency of tuberculous meningitis to occur during the active stage of a primary lesion is further corroborated in a study of the chest X-ray films of children dying with tuberculous meningitis as shown below. Of the 160 cases with chest roentgenograms, 76.9 per cent showed primary tuberculosis without calcification.

Last roentgenograms of children dying of meningitis—167 cases

Manifest primary tuberculosis.....	123
Enlarged nodes containing calcification.....	3
Calcification of parenchyma or nodes or both.....	13
Pleurisy with effusion.....	2
Pleurisy and hematogenous pulmonary tuberculosis.....	1
Hematogenous tuberculosis only.....	7
Negative X-ray films.....	11
No X-ray films*.....	7

* One case showed caseous primary tuberculosis on postmortem examination.

AUTOPSY EVIDENCE OF AGE OF PRIMARY TUBERCULOSIS IN
CHILDREN DYING OF MENINGITIS

Further evidence that meningitis most commonly occurs while the primary tuberculous lesion is fresh is obtained from autopsy evidence. Sixty-four cases had postmortem examinations of the lungs and caseous primary complexes were found 48 times. Caseous mediastinal nodes but no primary parenchymal foci were found in 3 additional cases.

Eight cases had encapsulated primary lesions, 3 of them showing calcification and an additional 3 cases whose primary foci could not be identified had calcifying caseous nodes. One child, who had been known to us with a primary tuberculosis of the left upper lobe four years before death, showed only a fibrotic left upper lobe; and in another child with a very extensive miliary tuberculosis of the lungs no evidence of a primary focus or regional nodes could be discovered.

We, therefore, have no evidence of encapsulation or calcification in the primary focus or regional nodes in 51 of 64 cases, or 79.7 per cent. Of the 12 cases which showed fibrosis, encapsulation or calcification of the primary focus, 9 had been known prior to the development of the meningitis. Of these cases, 6 had been followed for fifteen months to eleven years; the remaining 3 cases had been known only for short periods, one for seven months and 2 for ten weeks. The case known for seven months was 2-years-old at the time of death, and the primary focus was described as a large caseous focus with "sharply defined organized capsule." In the 2 cases known only for ten weeks, who were 14-months and 2-years-old, the capsule was not as well defined and calcification was only found on microscopic examination. X-ray and postmortem diagnosis agreed fairly consistently. In only 4 cases was there a difference in

the estimate of the freshness of the lesion by the two examinations. Two cases which were called fresh primary foci on X-ray appearance showed calcifications, one grossly and one microscopically. A third primary focus, judged on X-ray examination to be fresh, was encapsulated. Another primary lesion which cast a small round dense shadow on X-ray films was called calcified and on autopsy proved to be well encapsulated but contained no calcium.

It would seem from the evidence presented from clinical histories and by X-ray and autopsy examination that in our cases tuberculous meningitis tended to occur early in the course of the disease, the majority of cases occurring six months or less after the onset; and over 75 per cent showing evidence of a fresh primary lesion.

OCCURRENCE OF HEMATOGENOUS TUBERCULOSIS WITH MENINGITIS

Chart 6 shows the incidence of miliary tuberculosis in our cases of meningitis. It is evident that hematogenous tuberculosis coincided with meningitis more

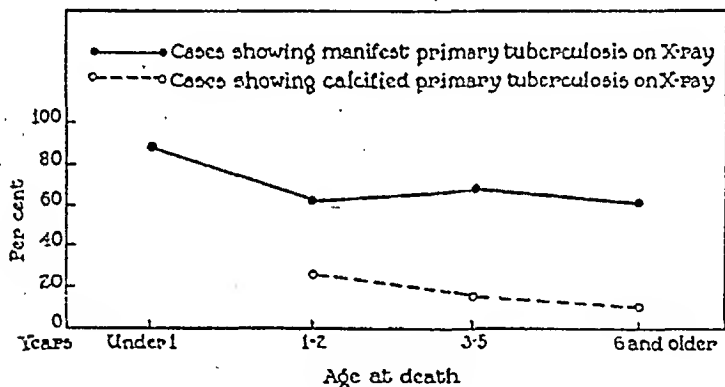


CHART 6. Occurrence of miliary pulmonary tuberculosis in 139 cases of tuberculous meningitis.

often in the infants under one year than in older children. It is also obvious that miliary tuberculosis was many times more frequent in children dying of meningitis while the primary lesion was fresh than after the focus had shown evidence of calcification. Of the 123 cases with manifest primary tuberculosis and tuberculous meningitis, 84 showed, in addition, roentgen evidence of hematogenous pulmonary tuberculosis. Of the remaining cases, in which no miliary lesions could be seen on X-ray films, there was evidence of miliary pulmonary tuberculosis on postmortem examination in 2 cases and, in an additional 5 cases where no pulmonary hematogenous seeding was found either on X-ray or postmortem examination, extrapulmonary miliary tubercles were found. Therefore, 91, or 73.9 per cent, of the cases of meningitis with fresh primary tuberculosis had roentgen or postmortem evidence of hematogenous dissemination. Only 3 of the 16 cases with roentgen evidence of *calcifying* primary foci showed miliary tuberculosis on X-ray examination. One additional case, with no X-ray evidence of miliary tuberculosis, had a few miliary tubercles in the liver,

spleen and kidney on autopsy, but none were found in the lungs. Therefore, only 25 per cent of the meningitis cases with calcifying primary foci had evidence of hematogenous dissemination.

The association of miliary tuberculosis and meningitis is also demonstrated in the cases of miliary tuberculosis seen in the Children's Medical Service of Bellevue Hospital. In a group of 122 cases of miliary tuberculosis, 81, or 66.4 per cent, died with clinical evidence of meningitis, and, of 72 cases of miliary tuberculosis who were examined postmortem, 44, or 61.1 per cent, had meningitis.

DISCUSSION

The explanation of the pathogenesis of tuberculous meningitis presented by Rich and McCordock has been accepted by many pathologists. In our series of cases we have limited pathological evidence of the existence of older caseous foci in the brains or meninges of children dying of tuberculous meningitis, since many of our cases died before Rich and McCordock's study was published and detailed examination was not always made. In 46 of 65 cases the pathologist stated that older caseous foci were sought and they were found in 16 cases, or 34.8 per cent. From the evidence of Rich and McCordock, and MacGregor and Green there would seem to be little doubt that, in carefully studied cases of meningitis, a previously established caseous focus can usually be demonstrated in the cortex, meninges or adjacent bone structures.

With the rapid development of new drugs which prove valuable in combating the tubercle bacillus *in vitro* and in experimental animals, hope of successfully treating tuberculous meningitis becomes more likely. Cases must be recognized early if we are to cure the disease without leaving a damaged brain. Evidence has been presented which suggests a correlation between the duration of tuberculous meningitis and the development of hydrocephalus. Since the object of therapy is recovery without residual damage we must learn to diagnose meningitis early. Obviously the children who have the best chance of having their disease recognized early will be those who are known to have tuberculosis and who are under close supervision in a hospital or at home. The question of the regular supervision of cases of asymptomatic primary tuberculosis was of academic interest only when no specific therapy could be offered in the event of early diagnosis of tuberculous meningitis. With the hoped for advent of specific therapy and possible cure as a reward for early diagnosis of meningitis, supervision of all cases of active primary tuberculosis, whether or not they are accompanied by symptoms, should become universal.

SUMMARY

In preparation for specific therapy of tuberculous meningitis by drug or antibiotic, an analysis of 167 cases of meningitis seen in the Chest Clinic of the Children's Medical Service of Bellevue Hospital has been undertaken.

1. As in other series, the disease was found to occur most commonly in the spring.

2. Of the cases first seen with meningitis, 54.6 per cent were less than 2-years-old and 80 per cent were under 4 years of age. In contrast, only 32.6 per cent of the children who developed meningitis while under treatment for primary tuberculosis developed meningitis under the age of 2 and 63 per cent under 4 years of age.

3. Anergy to tuberculin was found to be relatively uncommon even in well developed cases of meningitis; 85 per cent of the patients in whom readings of tuberculin tests were obtained were positive.

4. General symptoms such as vomiting, apathy or drowsiness were the most usual first symptoms observed. Irritability was more commonly noted as an early symptom in cases developing on the ward than at home. Headache rarely occurred under 4 years of age, but was observed in 60 per cent of cases over that age. Convulsions appeared twice as often in the child not suspected of tuberculosis as in the child known to be tuberculous. The average age of children having generalized convulsions with meningitis was 19 months.

5. The duration of meningitis from onset of symptoms to death varied from one to sixty-three days. The average duration was nineteen and one-half days.

6. Hydrocephalus was found in 22.5 per cent of the autopsied cases which lasted less than three weeks after the initial symptom and in 63.6 per cent of autopsied cases which survived more than three weeks after the first symptoms of meningitis. This emphasizes the importance of initiating any treatment as early as possible.

SUMARIO

Meningitis Tuberculosa en el Niño, con Referencia Particular a la Forma Serosa: 1ª Parte. Meningitis Tuberculosa

Como preparación para la terapéutica específica de la meningitis tuberculosa con antibióticos u otras drogas, se emprendió un análisis de 167 casos de meningitis observados en la Clínica Torácica del Servicio Médico de Niños del Hospital Bellevue de Nueva York.

1. Lo mismo que en otras series, la enfermedad se presentó más a menudo en la primavera.

2. De los casos que ya tenían meningitis al ser observados por primera vez, 54.6 por ciento tenían menos de 2 años de edad y 80 por ciento menos de 4 años. En contraposición, de los niños que manifestaron meningitis mientras se les trataba por tuberculosis primaria, sólo 32.6 por ciento tenían menos de 2 años y 63 por ciento menos de 4 años.

3. La anergia a la tubereulina resultó ser relativamente rara aun en los casos bien desarrollados de meningitis; 85 por ciento de los enfermos en quienes se hicieron lecturas de pruebas a la tubereulina, resultaron positivos.

4. Los primeros síntomas observados más habitualmente fueron generales, como vómitos, apatía o somnolencia. La irascibilidad fué notada más frecuentemente como síntoma temprano en los casos que se presentaron en la sala que en los tratados a domicilio. Rara vez se presentó cefalalgia en los de menos de 4 años, pero fué observada en 60 por ciento de los mayores de dicha edad.

Las convulsiones se presentaron dos veces más a menudo en los niños en que no se sospechaba tuberculosis que en aquellos reconocidamente tuberculosos. La edad de los niños que tuvieron convulsiones generalizadas con meningitis promedió 19 meses.

5. La duración de la meningitis desde la iniciación de los síntomas hasta la muerte varió de uno a 63 días, promediando 19 1/2 días.

6. Se descubrió hidrocefalia en 22.5 por ciento de las autopsias de los casos que habían sobrevivido menos de 3 semanas después de presentarse el sintoma inicial y en 63.6 por ciento de los que sobrevivieron más de 2 semanas, lo cual recalca la importancia de iniciar el tratamiento lo más antes posible.

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TUBERCULOUS MENINGITIS IN CHILDREN^{1,2}

With Special Reference to Serous Meningitis

Part II. Serous Tuberculous Meningitis

EDITH M. LINCOLN

In the previous paper, 167 cases of tuberculous meningitis observed in the Chest Clinic of the Children's Medical Service of Bellevue Hospital were analyzed.

In contrast to the child with tuberculous meningitis who in our series invariably died of his disease, we have seen children with physical signs and symptoms very suggestive of tuberculous meningitis some of whom apparently recovered completely.

MacGregor and Green (1) reported 2 cases of tuberculosis in young children in whom there were transient neurological signs suggesting tuberculous meningitis. In both, the spinal fluids on a single occasion produced a web and cytological changes suggestive of tuberculous meningitis but no tubercle bacilli were found. Subsequent spinal fluids were normal and these cases recovered completely. The authors suggested that the symptoms might have been due to localized foci in the cortex or meninges which did not progress sufficiently to cause a fatal meningitis.

These same authors found intracranial tuberculous foci in 11 out of 24 patients who died of tuberculosis without meningitis. In 3 of these cases no hematogenous foci were found elsewhere. They also found tubercle bacilli in 10 spinal fluids of the same group of tuberculous cases without meningitis. MacGregor and Green conclude that:

"Localized lesions in the central nervous system may be set up by hematogenous infection of a mild sporadic type, not meriting the name of miliary tuberculosis. There is evidence that on such occasions tubercle bacilli may be present, probably temporarily, in the cerebrospinal fluid, that occasionally clinical symptoms and signs may mark the occurrence of this initial infection and that such incidents are not necessarily followed by the development of fatal tuberculous meningitis."

Rich (2) mentions 2 cases in which there were transient signs of meningeal irritation some weeks before diffuse meningitis appeared. In each case the subsequent meningitis was due to a caseous cortical focus extending to the meninges. Cohen and Wood (3) describe 5 cases of "cerebral paratuberculosis" lasting one to two weeks, occurring in patients with exudative tuberculosis of recent origin. Fever, headache and drowsiness were the main symptoms; sluggish pupillary reactions and diminished or absent knee jerks were the chief physical signs; the spinal fluids were normal except for increase in pressure; all

¹ From the Chest Clinic of the Children's Medical Service, Bellevue Hospital, and the Department of Pediatrics, New York University, New York, New York.

² Aided by a grant from the National Tuberculosis Association.

cases recovered. The authors ascribe the clinical picture to an acute exudative reaction localized in the cerebral meninges.

It is my belief that the following cases reported as serous tuberculous meningitis are similar to those of MacGregor and Green, and Rich, and probably to those reported by Cohen and Wood; and are due either to the perifocal reaction around seedings in the early primary or postprimary stages or to later collateral inflammation around older caseous foci in the cortex or meninges.

We shall present pathological evidence in cases VIII, X and XI that such foci may be found without meningitis in children who had presented the picture of tuberculous serous meningitis. Moreover, 2 cases, VI and VII, will be presented in which postmortem examination made eighteen and thirty-two months after the serous meningitis showed adhesive nonspecific meningitis.

The clinical picture of tuberculous serous meningitis is not uncommonly seen on a ward for children with active tuberculosis. However, serous meningitis may be secondary to other conditions, as well as tuberculosis, and an effort has been made to eliminate cases in which a nontuberculous infection has also been present. In addition, fatal cases have been omitted in which a tentative diagnosis of serous meningitis was made where no spinal taps were done in the last week of life and no autopsy was obtained. This leaves 12 cases for analysis. Of these, 3 are living and well, 4 died of tuberculosis while still showing symptoms of serous meningitis; in 3 of these last cases we have autopsy evidence of the absence of tuberculous meningitis. Four cases lost all neurological signs but died four to thirty-two months later of tuberculosis with no recurrence of symptoms suggesting meningitis. In 2 of these cases we have autopsy evidence of a previous nonspecific meningitis. One case recovered from a serous meningitis and died three months later of typical tuberculous meningitis.

The differentiation from tuberculous meningitis in most cases could only be made by examination of the spinal fluid and by the course of the disease. In many cases the spinal fluid pressure was increased and the cell count varied from 0 to 235 cells per cmm. No changes in chemical constituents were found. The sugar, protein and chlorides were within normal range; the lowest sugar recorded³ was 56 mg. per cent, the highest protein 39 mg. per cent. No pellicle was found in any of the spinal fluids and no tubercle bacilli were found as in the cases reported by MacGregor and Green. However, if our interpretation of the pathogenesis of serous tuberculous meningitis is correct, the finding of a few tubercle bacilli is not incompatible with the diagnosis of serous tuberculous meningitis.

CASE HISTORIES OF CHILDREN WITH SEROUS TUBERCULOUS MENINGITIS

Case I: A. P., an 11-year-old white boy, was admitted to the hospital on 10/23/34 with signs of effusion in the right chest. His spleen was not palpable. White blood count was 6,200 with 70 per cent polymorphonuclear cells. Pleural fluid contained 2,600 cells per cc. practically all lymphocytes. Mantoux test was positive with 0.01 mg. of tuberculin. Gastric lavage was negative for tubercle bacilli. Irregular fever persisted for over ten

³ The one possible exception is discussed under case IX.

weeks; the signs cleared slowly with definite evidence of fluid still present eight weeks after onset. Twelve weeks after admission, 1/21/35, after temperature had been below 100°F. for two weeks, the patient developed slight cough and acute pain in left chest anteriorly, radiating to shoulder. He became acutely ill and on 1/24/35, three days later, developed signs of fluid in the left chest, fever to 103°F. and frontal headache. All deep reflexes were hyperactive and a transient left ankle clonus was obtained. From 1/25/35 to 1/27/35 headache continued to grow worse and was increased by flexion of neck which was definitely stiff. At this time the deep reflexes were normal; Kernig and Brudzinski tests were negative; there was a well sustained left ankle clonus; eye grounds were normal; the child was very drowsy and stuporous. On 1/28/35 the spinal fluid was clear, under increased pressure without cells; sugar 60 mg. per cent, protein 14 mg. per cent, chlorides 620 mg. per cent, no pellicle formation was noted. The headache was relieved by tap for twelve hours and then recurred. The patient continued very drowsy but could be roused and his neck was less stiff; the spleen was definitely palpable; temperature continued to reach 103° or 104°F. daily. On 1/31/35, ten days after onset of serous meningitis, a second spinal tap showed a cell count of 35 per cmm. with 75 per cent lymphocytes; sugar 77 mg. per cent, protein 25 mg. per cent, chlorides 706 mg. per cent, no pellicle formation; no tubercle bacilli were found. Inoculation of fluid into a guinea pig was later reported to be negative for tubercle bacilli. During the next few days the headache improved, the patient was less drowsy and neurological examination was entirely normal except for bilateral ankle clonus. On 2/5/35, two weeks after onset, the spinal fluid showed a count of 20 cells per cmm. with 90 per cent lymphocytes; sugar 62 mg. per cent, protein 23 mg. per cent, chlorides 742 mg. per cent. The temperature gradually fell to normal and stayed so after 2/26/35. The spleen was not felt after 3/1/35. The bilateral clonus persisted until 2/19/35 but no other abnormal neurological signs were present. The signs of fluid in the left chest began to diminish about the middle of January and by 4/15/35 only dullness and diminished breath sounds persisted at the base. This boy was sent to a sanatorium for seventeen months. He has been followed in the clinic since his discharge and has remained well; eight years after the episode of serous meningitis this boy was accepted in the Army and served in the Pacific area for over a year.

Case II: J. G., a 6-year-old white boy, was admitted to the hospital on 3/25/35. One brother had died of tuberculous meningitis. For two weeks before admission he had been "lying around" and his mother noted that he tired easily and seemed feverish. He cried out at night complaining of pain in his head. He had vomited several times. On admission he was drowsy and looked chronically ill. The next day he had a positive bilateral Kernig sign and the Mantoux test with 0.1 mg. tuberculin, which had been done in the dispensary the day before admission, was vesiculated and markedly indurated. X-ray examination showed a large left root shadow with clouding extending to axilla (figure 1A). Spinal fluid was under markedly increased pressure with 2 cells per cmm., sugar 76 mg. per cent, protein 18 mg. per cent, chlorides 678 mg. per cent. Inoculation of fluid into a guinea pig gave no evidence of tuberculosis. The white blood count was 9,000 with 71 per cent polymorphonuclear leucocytes. Shortly after the spinal tap the Kernig sign disappeared and the neurological examination remained negative thereafter. During the first week in the hospital his temperature fluctuated widely from 98° to 101° or 103°F. daily, but thereafter never reached 101°F. This boy remained under observation at Bellevue for six weeks and was transferred to a sanatorium where he remained seven months. The primary focus of tuberculosis in his lung healed, leaving definite calcification (figure 1B). He is now 17 years old and in apparent good health.

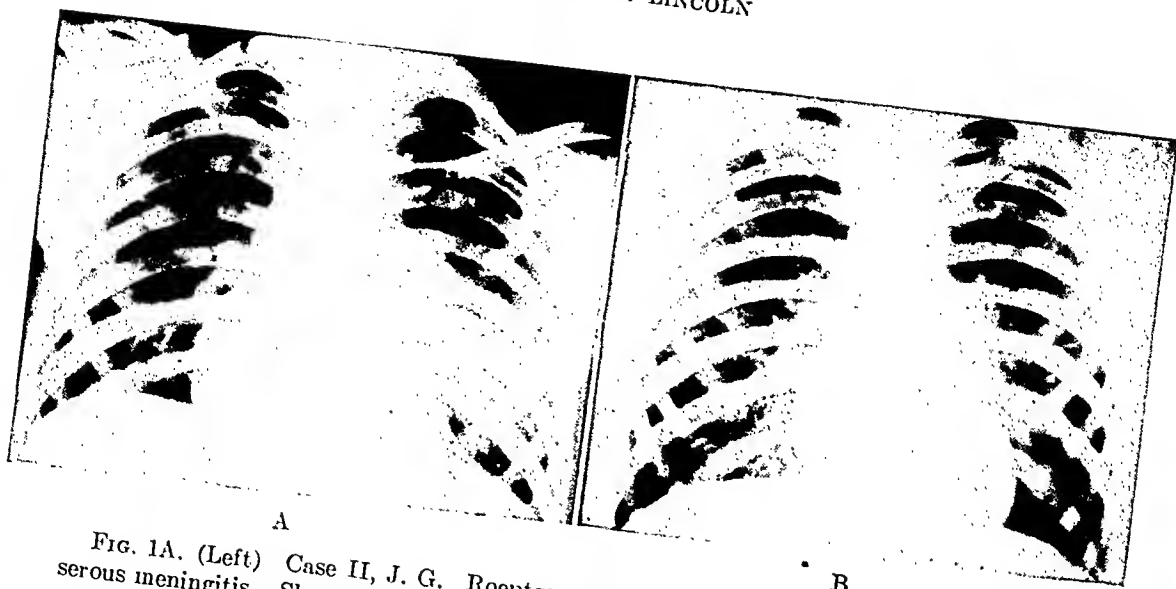


FIG. 1A. (Left) Case II, J. G. Roentgenogram taken on admission to hospital with serous meningitis. Shows a large left root with clouding extending to axilla, interpreted as a primary complex of tuberculous.

FIG. 1B. (Right) Case II, J. G. X-ray film taken six years later, showing calcification in third left interspace behind fourth rib and in left root.

Case III: R. P., a 14-months-old Porto Rican boy, probably had the onset of his primary tuberculous in July, 1931. He was admitted to Bellevue Hospital on 9/24/31 and was found to be a well developed and nourished infant with a positive tuberculin test and X-ray evidence of only a slight widening of the mediastinum to the right (figure 2A). He had fever associated with an upper respiratory infection from 9/28/31 to 10/4/31. His temperature then remained normal from 10/5/31 to 10/14/31, when it began to fluctuate daily to between 103° and 104°F. He had no evidence of a cold and did not appear to be acutely ill. An X-ray film taken 10/19/31 showed an increase in the width of the mediastinum to the right and a clouding extending to the base (figure 2B). At this time he had dullness and diminished breath sounds at the right base posteriorly. On 10/20/31 he became acutely ill, had slight dyspnea and dilatation of *alae nasi*. Small moist râles were heard in the right interscapular region. His neck was stiff and knee jerks hyperactive, otherwise the neurological examination was negative. The spinal fluid was under markedly increased pressure; no cells were seen; sugar was 56 mg. per cent, protein 18 mg. per cent. Inoculation of fluid into a guinea pig gave negative results. He continued to be irritable and on 10/23/31 there was definite rigidity of the neck, all superficial reflexes were hyperactive and ankle clonus was markedly positive on both sides. High daily temperature persisted for eight days. During this time his total white blood count was 10,000 with 60 per cent PMN. An X-ray film taken 10/24/31 showed a further increase in the size and density of the lesion at the right base and this persisted unchanged for one month (figure 2C). By 10/26/31 neurological examination had become negative and râles could no longer be heard. When first seen for follow-up supervision in the dispensary in April, 1934, over two years after his hospital admission, an X-ray film showed irregular streaking and mottling extending from the right root to the diaphragm and small calcifications were seen within this area (figure 2D). This boy is now 16 years old and is in good health.

These 3 boys all had transient neurological symptoms suggesting cerebral irritation while suffering from active tuberculosis. In the first case the meningeal sign coincided with the development of a pleural effusion and in the third case with an increase in the size of the perifocal reaction around the pri-

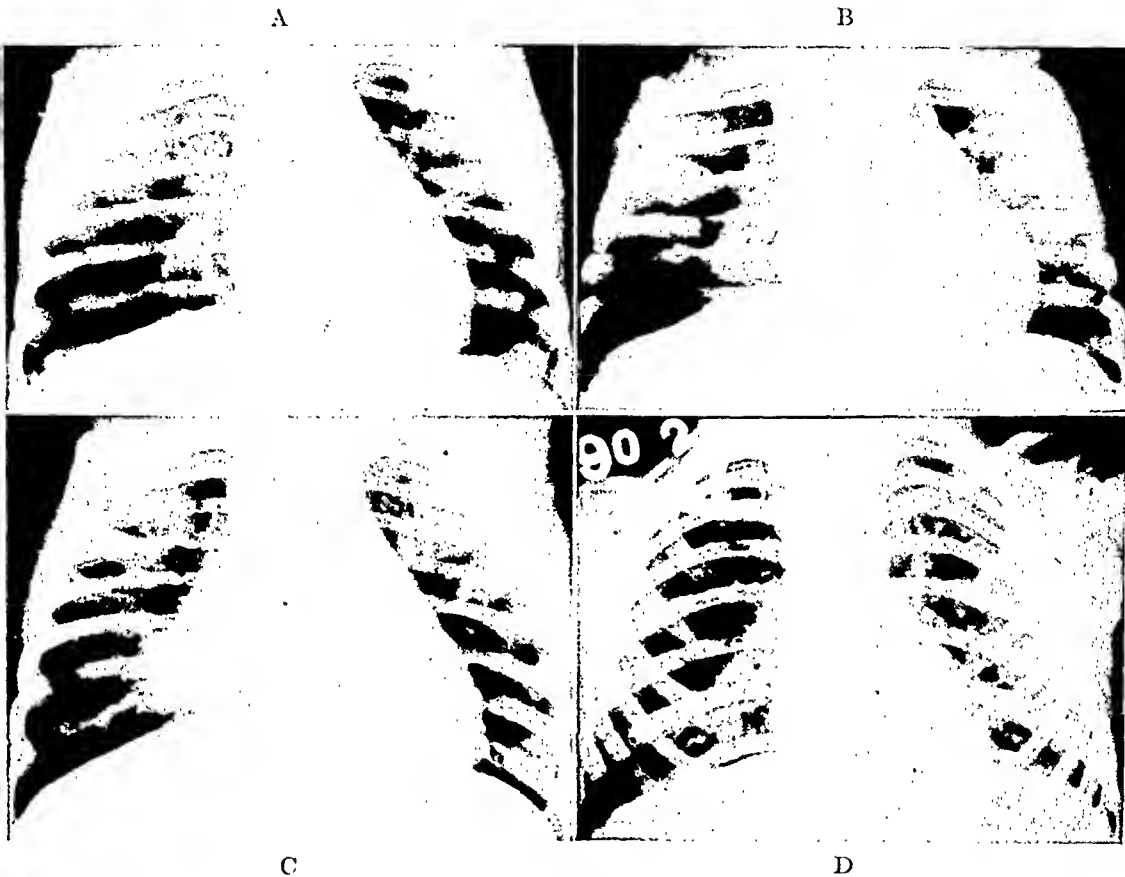


FIG. 2A. (Upper left) Case III, R. P. X-ray film taken on admission to hospital 9/24/31, showing a very slight widening of the mediastinum to the right.

FIG. 2B. (Upper right) Case III, R. P. X-ray film taken 10/19/31 after five days of high fever, showing an increase in width of the mediastinum to the right and clouding extending from right root to base.

FIG. 2C. (Lower left) Case III, R. P. X-ray film taken 10/24/31, four days after acute onset of serous meningitis, showing further increase in size and density of clouding from right root to base. Moist râles were heard in the right interseapular area from 10/20/31 to 10/26/31.

FIG. 2D. (Lower right) Case III, R. P. X-ray film taken in 1934, showing calcification within streaked and mottled area extending from right root to base.

mary focus. In case I, I think we can assume that the pleural effusion on the left was due to a perifocal reaction around previously seeded tubercles of haematogenous origin and it seems not unreasonable to surmise that in cases I and III the signs of cerebral irritation may have been due to similar collateral

reactions around fresh or previously seeded tuberculous foci. In case II, we did not see the development of the clinical picture which made the admitting physician suspect meningitis. His case history has been included because it is representative of a group of cases which we surmise but cannot prove are due to the postprimary lympho-hematogenous seeding of tubercle bacilli into the cortex. During the postprimary lympho-hematogenous seeding of tubercle bacilli we know that the superficial lymph nodes and the spleen may become palpable for varying periods of time and it seems not unreasonable to think that seedings of similar origin into the cortex might result in the clinical picture that case II presents.

We have records of 4 tuberculous children who presented briefly the picture of serous meningitis and died without a recurrence of meningeal signs four to thirty-two months later.

Case IV: A. W., a Negro girl 5 years old, was admitted 3/22/31 with primary pulmonary tuberculosis, tuberculous cervical adenitis, interstitial keratitis and tuberculous peritonitis. For one month her temperature did not exceed 100° F. and, then, on 4/24/31 she had a sharp rise in temperature to 103° F. which persisted for six days. At this time papulonecrotic tuberculides were first noted over the trunk and extremities. Shortly after the onset of fever she became drowsy and listless and vomited once. White blood cells at this time were 10,000 with 76 per cent polymorphonuclear cells and 17 per cent small monocytes. Vomiting, which had been so severe that not even water was retained, stopped spontaneously on 5/4/31. A lumbar puncture was done at this time because of the suspicion of an early tuberculous meningitis. It showed a clear fluid with 6 cells per cmm., sugar 62 mg. per cent, protein 22 mg. per cent. The neurological examination remained entirely negative until 5/6/31 when bilateral, well sustained ankle clonus appeared. A chest X-ray film taken at this time showed an increase in the area of infiltration surrounding the right root. One week later the neurological examination was again entirely normal and the child seemed alert. She continued to have occasional rises of temperature, crops of papulonecrotic tuberculides and active interstitial keratitis. She died 9/29/32 after having been transferred to another hospital. She had no recurrence of meningeal signs and the last chest X-ray film taken 9/7/32 showed very little change from our film of 5/5/31 and no evidence of miliary tuberculosis.

Case V: S. S., a Negro girl 3 years old, was admitted to Bellevue Hospital on 7/11/31 for treatment of tuberculous keratitis. Because of irregular high fever she was transferred to the Pediatric Service on 8/9/31. She showed marked phlyctenular conjunctivitis and keratitis and a distended abdomen with a very large liver. A greatly enlarged right root with no evidence of parenchymal involvement was seen on her X-ray film. This child was quiet but not drowsy. The development of meningitis was anticipated and her chart contains frequent notes stressing the absence of neurological signs. On 10/22/31 she became very drowsy and irritable and in spite of absence of other neurological signs a spinal tap was done. The fluid was clear, under normal pressure with 3 cells per cmm., sugar 60 mg. per cent, protein 22 mg. per cent. The following day there was a slightly stiff neck, hyperactive knee jerks, a bilateral ankle clonus. Her condition remained unchanged for forty-eight hours, then the neurological signs disappeared and never recurred. She was very drowsy and irritable for about two weeks, then became much more alert,

although there was no improvement in the abdominal condition. She was discharged to Sea View Hospital 2/9/32 and died there four months later of tuberculous peritonitis without having any recurrence of neurological signs.

Case VI: C. P., a Negro girl of 6 years, had an acute onset of fever six weeks before admission and subsequently developed anorexia and apathy and lost 5 pounds in weight. On admission to the hospital on 10/22/30 she was not acutely ill. X-ray examination of the lungs showed a marked widening of the mediastinum to the left and an infiltration at the right base adjacent to the heart. She had a general enlargement of the superficial lymph nodes including a large left supraclavicular node and a markedly distended abdomen in which several small hard masses could be palpated; the spleen and liver were enlarged; a flat film of abdomen and gastro-intestinal X-ray series were negative. Urine showed a faint trace of albumen, white cells, sometimes clumped, a few red cells and on one occasion granular casts. Complete urological examination, including retrograde pyelograms, was negative.

Neurological examination remained negative until 11/16/30. On this day the fever rose to 104° F. The neck was stiff; Kernig and Brudzinski signs were negative but there was a bilateral marked ankle clonus. There was no drowsiness nor irritability. On 11/24/30 she still showed a bilateral ankle clonus "sustained to about 10 contractions." A spinal tap revealed a clear fluid under normal pressure, no cells, sugar 54 mg. per cent, protein 12 mg. per cent. On 12/5/30 the ankle clonus on the right side was barely obtainable, but was still well sustained on the left. Two weeks later this child was transferred to Sea View Hospital where she remained sixteen months. She continued to have fever for months but we have no information about her neurological examination beyond the fact that no deviations from normal were noted. She returned to our dispensary in April, 1932 in excellent general condition but with evidence of fresh phlyctenular conjunctivitis of her right eye. X-ray films showed calcification in the parenchyma just adjacent to right cardiac border and above the first left rib. No enlargement of the mediastinum could be made out. She remained well until January, 1933 when she reported to the eye clinic because of a recurrence of phlyctenules. A Mantoux test was followed by a marked local reaction and high fever for several days. One month later she developed *erythema induratum* on both calves, fever and an enlargement of her superficial lymph nodes. She was readmitted to the hospital, developed signs of uremia with a blood non-protein nitrogen of 150 mg. per cent and also a positive Congo red test. On 6/22/33 she showed numerous papulonecrotic tuberculides which continued to appear till death on 7/4/33. Neurological examination remained entirely normal till three days before death when a stiff neck was noted. Spinal fluid was clear, under normal pressure with no cells seen, sugar 72 mg. per cent, protein 35 mg. per cent. Following the spinal tap the neck was no longer stiff. An autopsy on this child (Dr. W. Gretlmann) revealed a primary tuberculous focus in the left lower lobe with incomplete capsule formation; caseous bronchopulmonary tracheobronchial and paratracheal lymph nodes especially on the left side; productive tuberculosis of the colon with caseous and calcified lymphadenitis of the mesenteric and retroperitoneal lymph nodes; amyloidosis of kidney, spleen and liver. Examination of the brain (Dr. Irving Graef): "The dura strips readily and the underlying pia arachnoid presents fine adhesions to it in places. Multiple sections of the entire brain and brain stem disclose no abnormalities except for marked congestion of the blood vessels. There appears to be some resorption in the white matter about the blood vessels. The ventricles are symmetrical and contain clear fluid. Diagnosis: Healed, nonspecific focal basilar meningitis."

Case VII: C. W., a Negro boy of 2, had the onset of his primary tuberculosis in October, 1931 followed in eleven weeks by generalized miliary tuberculosis.⁴ He was admitted to Bellevue Hospital on 4/9/32 in apparently excellent state of nutrition, with constant normal temperature. Physical examination of the lungs was normal. The liver and spleen were enlarged. There was a general enlargement of the superficial lymph nodes. X-ray films of the chest showed marked widening of mediastinum to left and miliary nodules throughout both lungs. On 4/26/32 a number of papulonecrotic tuberculides appeared on his extremities and trunk and these recurred in waves for a period of four months. The temperature continued normal. On 5/21/32 there was sudden onset of fever, apathy and irritability when aroused. Kernig sign was present on the right; there was a marked tremor of the hands, and the child cried out when an attempt was made to flex his neck. On 5/24/32 the neurological signs persisted and the neck was rigid. A spinal fluid taken at this time was clear, under increased pressure; 4 lymphocytes per cmm., sugar 103 mg. per cent, protein 26 mg. per cent. On 5/27/32 X-ray signs of consolidation appeared over the left upper lobe. On examination there was dulness with tubular breath sounds and a few moist râles. The high fever persisted until 6/12/32, then a low grade fever till 7/1/32 and thereafter the temperature returned to normal. The physical signs over the left upper lobe cleared entirely by 5/31/32 but the X-ray shadow persisted or three months and then cleared to a great extent. By 5/31/32 stiff neck was the only remaining abnormal neurological sign and this disappeared twenty-four hours later. The miliary pulmonary tuberculosis gradually receded, calcification appeared on X-ray films in the mediastinal nodes and also in the spleen. The boy remained well nourished with normal temperature until 11/23/33 when he again became acutely ill and died in four days. The X-ray film taken on the day of death showed a diffuse shadow in the right upper lobe. Spinal fluid three days before death was clear with diminished pressure, 2 lymphocytes per cmm., sugar 78 mg. per cent, protein 22 mg. per cent, chlorides 684 mg. per cent. Inoculation of fluid into a guinea pig gave negative results. Autopsy (Dr. W. Grethmann) showed, in addition to a calcified tuberculous primary focus of the right upper lobe, extensive caseous and calcifying tuberculosis in lymph nodes, and a chronic hematogenous tuberculosis of the lungs, liver, spleen and kidneys in various stages of caseation, fibrosis and calcification. He had a tuberculous bronchopneumonia of the right upper lobe and a purulent pericarditis. Section of the area in the left lung which was involved simultaneously with the appearance of the serous meningitis showed scar formation with caseous areas.

Examination of brain (Dr. W. Grethmann): "When taking out the brain, considerable difficulty is encountered on account of adhesions of the dura with the pia over and between the anterior poles of both hemispheres. The brain can only be taken out by cutting the dura. The ventricles do not contain an unusual amount of cerebrospinal fluid. A careful search through the area of the stem ganglia, the cortex of both hemispheres of the cerebellum does not show signs of tuberculous foci. Diagnosis: Adhesive meningitis at the anterior poles of both hemispheres."

Again in some of these cases we note the tendency for the signs of serous meningitis to be associated with evidence of spread of the tuberculous disease locally or by the hematogenous route. In case IV the appearance of papulonecrotic tuberculides coincided with the serous meningitis and there was an increase in the area of pulmonary infiltration, as seen on X-ray films. In

⁴ This boy has been previously reported to illustrate various aspects of his disease (Amberson (4), Lincoln (5)).

case VI there was simultaneous appearance of a tuberculous pneumonia and signs of meningeal irritation. In both cases VI and VII, autopsy showed a nonspecific adhesive meningitis with no evidence of caseous cortical foci.

We have records of 4 cases whose signs of meningeal irritation persisted till death.

Case VIII: M. H., a Negro girl of 23 months, with extensive primary tuberculosis of the left upper lobe complicated by pleurisy, pericarditis and hematogenous dissemination, was first admitted to Bellevue Hospital on 12/18/31. Soon after admission she had a high fever for ten days and an increase in the hematogenous lesions seen on X-ray films. During February and March she did not seem acutely ill; she had a low-grade fever and gained weight. At the end of March her liver and spleen enlarged markedly, and papulonecrotic tuberculides appeared on the wrists and right hand. Early in April, daily high fever recurred and moist râles were heard in both lungs. On 4/15/32, four months after admission, neurological examination was negative. One week later she developed a slightly stiff neck and photophobia and a questionably positive bilateral Kernig sign. The stiffness of the neck continued and the child continuously lay on her right side with knees rigidly flexed. A bilateral ankle clonus appeared on 4/23/32. Spinal fluid was clear and under normal pressure; one cell per cmm.; sugar 77 mg. per cent, protein 22 mg. per cent. On 4/27/32 a second spinal fluid showed only one cell per cmm., sugar 68 mg. per cent, protein 24 mg. per cent. On 5/7/32 there were 160 cells per cmm., sugar 75 mg. per cent, protein 22 mg. per cent. Inoculations of fluids into guinea pigs were negative for tuberculosis. By 5/22/32 her legs could be extended without pain, there was only slight nuchal resistance. Four days later she became very irritable, the neck became rigid, she lay constantly on her right side with her right hand held at times in an athetoid position. At times she had a fine tremor of the right hand. She died with the neurological picture unchanged on 5/31/32 and the last spinal tap on 5/20/32 showed 12 cells per cmm., sugar 63 mg. per cent, protein 22 mg. per cent. No tubercle bacilli were found on direct examination or by guinea pig inoculation.

At autopsy, this child had a primary tuberculosis of the lung with generalized hematogenous tuberculosis. The brain showed "a rounded yellowish mass on the surface of the left parietal lobe. This mass measures about 6 mm. in its greatest diameter. It is attached to the under surface of the meninges and firmly adherent at the site of attachment. There are no miliary tubercles seen on the brain or meninges." (Dr. C. A. Connor.) In addition, Dr. W. Grethmann noted that "the inner surface of the dura mater is very rough, dull, and granular over both frontal poles of the hemisphere."

Case IX: A. J., a Negro girl of 3 years, admitted 11/16/30, had a large primary tuberculous focus of the right lower lobe, general lymph node enlargement and phlyctenular conjunctivitis and keratitis and recurrent papulonecrotic tuberculides. She ran an irregular fever but was in fairly good condition. Dulness and diminished breathing were the only signs heard over the base of the right lung. Five months after admission, on 5/3/31, she became acutely ill, drowsy and nauseated and complained of headache. For the first time constant moist râles were heard over the right base. The Kernig sign was positive and her neck slightly stiff. Spinal fluid was clear and under normal pressure, with 6 cells per cmm., sugar 58 mg. per cent, protein 22 mg. per cent. Her neck continued stiff and a positive Kernig sign persisted until death four weeks later. She developed a right ankle clonus and vomited occasionally. She became increasingly apathetic. Several spinal taps were done the last four days before death and revealed no abnormality. The

last spinal fluid showed a sugar of 88 mg. per cent and a protein of 22 mg. per cent. There was no X-ray evidence of miliary tuberculosis.

Case X: R. B., a white male 7 months old. Admitted 10/18/45, with X-ray films showing excavating primary tuberculosis of the right upper lobe and mottling throughout both lung fields. Moist râles were heard over his entire pulmonary areas. He had fever of low grade until 11/3/45 when he developed high temperature and a bilateral otitis media. This baby was obviously very ill but was not irritable and neurological examination remained entirely normal until 12/3/45 when a right facial palsy developed. The fontanelle was not full. There was no stiff neck nor other abnormal neurological sign. Examination of the spinal fluid was clear with 275 cells per cmm. with 92 per cent lymphocytes; sugar 75 mg. per cent, protein 39 mg. per cent, chlorides 660 mg. per cent. Examination of the right ear showed an "erosion of the supra-posterior canal wall into attic. Caseous detritus coming from this fistula." (Dr. J. F. Daly.) Biopsy of right middle ear tissue showed "the subepithelial tissue is diffusely and densely infiltrated with lymphocytes, plasma cells and large mononuclear cells. In some areas the large mononuclear cells are arranged in epithelioid fashion and there is a strong suggestion of tubercle formation. A rare multinucleated giant cell is present. No necrosis seen. An acid-fast stain demonstrates presence of several acid-fast bacilli. Diagnosis: Tuberculosis." (Dr. W. C. VonGlahn, Dr. J. W. Hall.) A second spinal tap done 12/10/45 showed a clear fluid with only one cell, sugar 83 mg. per cent, protein 43 mg. per cent, chlorides 715 mg. per cent. From 12/17/45 till death on 12/20/45 there was no stiffness of the neck but there was intermittent twitching at first of the right arm and both legs and later almost constant jerking of the head and extremities. Spinal tap done immediately after death showed a clear fluid with 8 lymphocytes per cmm., sugar of 25 mg. per cent,⁵ protein 39 mg. per cent, chlorides 802 mg. per cent. Culture was negative for tubercle bacilli as well as for other organisms. A postmortem examination showed no evidence of meningitis. Two caseous areas of tuberculosis, about 6 mm. in diameter, were present, one in the right frontal, one in the left fronto-parietal area.

This baby did not present the clinical picture of serous meningitis. Facial palsy was the only definite neurological sign which suggested the first lumbar tap. The spinal fluid showed definite evidence of meningeal irritation. Whether this was due to direct extension from the tuberculous middle ear or was secondary to a reaction around the areas of cortical caseation can only be surmised.

Case XI: J. Z., a 7-months-old white boy, whose illness began about 4/1/37 with fever, irritability, cough and weight loss, was admitted 5/3/37 with the diagnosis of lobar pneumonia. Mantoux test was positive with 0.1 mg. of tuberculin and an X-ray film showed consolidation of the right upper lobe. He looked chronically ill and had a daily fever to 104°F. Neurological examination was negative on 6/15/37. Three days later he developed a stiff neck and a positive Kernig sign. The spleen became palpable for the first time. There was X-ray evidence of hematogenous tuberculosis and an increase in the size of the primary focus. On 6/22/37 the spinal fluid showed 33 cells per cmm., all lymphocytes, sugar 68 mg. per cent, protein 22 mg. per cent, chlorides 696 mg. per cent.

⁵ This was the only instance of a chemical abnormality in any spinal fluid in any case of serous meningitis. Unfortunately our laboratory technician was ill and this examination was not done in our laboratory. The low sugar is incompatible with the normal protein and chloride content of the fluid and we are unable to evaluate its significance.

The neck varied in stiffness from this time on and was occasionally noted to be flexible. The baby became increasingly drowsy. On 7/6/37, four days before death, respirations were definitely of the Biot type. A postmortem spinal tap showed a clear fluid with 3 cells per cmm. Inoculation of fluid into a guinea pig gave negative results. On autopsy, this baby showed no evidence of meningitis either grossly or microscopically, but he did show caseous nodules in the left cerebellum and a similar area in the right occipital tip. Microscopic report (Dr. L. D. Stevenson): Hematoxylin and eosin stains of the occipital pole and cerebellum show a well demarcated area in the subcortical region. There is a large necrotic center with small areas of hemorrhage and surrounded by a zone of cellular exudate consisting of lymphocytes, large mononuclear cells, histiocytes and occasional multinucleated giant cells. There are many blood vessels in the region. There is perivascular and pericellular edema in the surrounding cortex. There is no evidence of meningitis."

This group of cases again illustrates the tendency for signs of tuberculous serous meningitis to follow or be accompanied by evidence of increased local activity of the pulmonary tuberculosis or of hematogenous seeding. In case VIII the neurological signs followed an increase in fever, occurrence of papulonecrotic tuberculides and the appearance of moist râles. Case IX likewise first had constant signs of moisture in the lung coincidentally with the evidence of meningeal irritation. In case XI the serous meningitis was accompanied by an increase in the size of the primary focus, X-ray evidence of hematogenous tuberculosis and the finding of a palpable spleen. In case X the evidence of serous meningitis provided by the spinal fluid might have been missed if the facial paralysis had not occurred.

If our explanation of the pathogenesis of serous tuberculous meningitis is correct, namely that the clinical picture is due to a perifocal reaction around a tuberculous focus previously established in the brain, then it is obvious that the clinical picture of serous meningitis may be seen preceding a tuberculous meningitis. However, in only one case was the clinical picture of serous tuberculous meningitis followed by a short remission of symptoms and then recurrence with caseous tuberculous meningitis and death.

Case XII: M. I., a Filipino boy 4 years old, was first examined as a contact to his father in October, 1938. He had a positive tuberculin test but a normal X-ray picture. Two months later he was reexamined because his sister had developed miliary tuberculosis and a roentgenogram showed a thickening of the left axillary pleura. On 12/26/38 he was admitted to Bellevue Hospital because of a low-grade fever. He had had a pneumococcus pneumonia with empyema and a complicating mastoiditis seven months previously and some discharge from his ear was still occasionally observed. He was a poorly nourished boy who showed a perforation in his left drum, and dulness and diminished breath sounds in his left axilla. His physical examination was otherwise essentially negative. An X-ray film taken on admission showed only thickening of the axillary pleura. During the first three weeks in the hospital the temperature only reached 101°F. on three occasions and was never above this. For the next two weeks his temperature rose almost daily to 102°F. X-ray film of 1/25/39 showed definite miliary tuberculosis of both lungs. The spleen was not felt, but he developed an enlargement of all the superficial lymph nodes; two weeks later, on 2/14/39, after his temperature had subsided for over a week, he suddenly com-

plained of pain in his back. His neck was definitely stiff and he gave evidence of pain on attempted flexion. Deep reflexes were hyperactive but no pathological reflexes were found although there was a suggestive ankle clonus. The spleen was palpable well below the costal margin. Spinal fluid was clear, sugar 64 mg. per cent, protein 35 mg. per cent, chlorides 702 mg. per cent. The stiff neck and hyperactive reflexes disappeared within the next twenty-four hours. He was transferred to Sea View Hospital on 3/30/39 and two days after admission his temperature rose, reaching 103°F. daily for twelve days. Shortly after the fever began he complained of pain in his neck for several days but this symptom subsided. A month later (4/29/39) he had an acute onset of headache, vomiting, associated with drowsiness and, on examination, had a bilateral ankle clonus. Spinal fluid on 5/1/39 showed 40 cells and a sugar of 41 mg. per cent. Within the next few days he developed rigidity of the neck, a positive Kernig sign and bilateral ankle clonus. On 5/9/39 the spinal fluid contained 210 cells, sugar was low and inoculation of fluid into a guinea pig was positive for tuberculosis. He died 5/16/39.

DISCUSSION

It is important that the clinical picture of caseous tuberculous meningitis and serous tuberculous meningitis be clearly differentiated. In the early stages they may have similar general symptoms. Vomiting, drowsiness or apathy, sudden rise in fever, irritability and headache are as commonly associated with the onset of serous meningitis as with tuberculous meningitis. Hematogenous tuberculosis is frequently seen in both types of meningitis and does not help in their differentiation. Signs of meningeal irritation, stiff neck, positive Kernig and Brudzinski signs are almost the rule in caseous meningitis but they may also be seen in serous meningitis so that these signs are of little value in differential diagnosis.

Marked early general symptoms with few neurological signs should suggest the possibility of a serous meningitis. Ankle clonus associated with some degree of nuchal inflexibility is the most common neurological sign in serous meningitis. Evidence of recent local extension of the pulmonary tuberculosis occurs more regularly with serous than with caseous meningitis. We have no record of a convulsion occurring in a case of serous meningitis, although several children had localized clonic movements or tremor of extremities. Involvement of the cranial nerves, except facial paralysis, which may be due to tuberculous otitis media, is also not recorded in our series of children with serous meningitis. Some cases have been very drowsy but none has been comatose. However, on clinical examination alone it is impossible to distinguish a caseous tuberculous meningitis from a serous tuberculous meningitis in the first stage of the disease. The differential diagnosis may often be difficult in the second stage, but in the third stage of caseous tuberculous meningitis the diagnosis should be obvious on clinical examination.

The spinal fluid offers an easier method of differential diagnosis. In either condition there may be increase in pressure and an increased number of cells, which are usually largely lymphocytes, but the sugar, protein and chloride content of the spinal fluid remains normal in serous meningitis. Tubercle bacilli have been reported in the spinal fluids of cases resembling the clinical

picture we are describing as serous meningitis. This finding in spinal fluid with a normal chemical content would therefore not offer a means of differential diagnosis between caseous and serous meningitis.

Temporary or complete recovery may follow serous tuberculous meningitis. Of the 12 cases presented in this paper 3 are alive and well, and 4 more recovered from serous meningitis but died four to thirty-two months later of other tuberculous complications. The spontaneous cure of tuberculous meningitis has been reported but even the most optimistic figures give the disease a mortality rate of over 99 per cent. In the twenty-five years since the Chest Clinic of the Children's Medical Service at Bellevue Hospital was organized, no case of spontaneous cure of tuberculous meningitis has been seen.

Cases have been presented showing evidence of cortical or meningeal irritation which we believe illustrate the clinical pictures associated with "Rich foci." It is my belief that some of the cases represent cortical seedings and in others the symptoms are due to collateral inflammation around previous seedings. We need more clinical observations before these two pictures can be clearly distinguished. Of the 4 cases which died while symptoms of serous meningitis were still present, in 3 instances the presence of caseous foci in the cortex and the absence of meningitis was proved by postmortem examination.

Cases have also been presented which suggest that, in common with other forms of tuberculosis, intracranial foci may be arrested and even healed. Three patients with serous meningitis were presented who are alive and well eleven to fifteen years later. Additional evidence of the possibility of disappearance of intracranial tuberculous foci is offered in the 2 patients who died eighteen and thirty-two months after their episodes of serous meningitis. Careful search failed to show intracranial caseous foci of tuberculosis, although in both cases there was evidence of healed nonspecific meningitis.

The prognosis of children who have recently had evidence of serous tuberculous meningitis must obviously be guarded if we believe that this clinical picture is due to caseous intracranial foci. As long as these foci remain active there is the ever present danger of discharge of tubercle bacilli into the subarachnoid space, causing a meningitis. In addition, there is often evidence of other foci of tuberculosis of hematogenous origin. If the child not only recovers from the serous meningitis but his underlying tuberculosis is apparently quiescent, every effort should be made for a period of years to guard him from factors which have been thought to precipitate a meningitis. It is possible that these factors, which have been discussed previously, act by causing a perifocal reaction around the area of cortical or meningeal seeding. A child who has had evidence of serous meningitis should therefore be guarded as much as possible against attacks of measles or pertussis; he should not have excessive exposure to sunlight and should never be subjected to further tuberculin testing. Surgical operations if not essential nor of life-saving nature should not be undertaken. Even with evidence of cortical seeding many clinicians, and notably Wallgren (6), believe that tuberculous meningitis may to some extent be prevented by limitation of the physical activity of the child during the most active phase of his primary tuberculosis.

SUMMARY

A clinical picture of meningeal irritation has been described which is not infrequent in children with active primary tuberculosis and which must be differentiated from tuberculous meningitis.

On clinical examination alone it may be impossible to distinguish a caseous tuberculous meningitis from a serous tuberculous meningitis in the first stage of the disease.

Spinal fluid examination offers the best means of differential diagnosis. In serous meningitis there may be an increase in pressure and increase in cells but the chemical content of the spinal fluid remains normal. The finding of a few acid-fast bacilli in the spinal fluid is not incompatible with the diagnosis of serous meningitis.

Twelve cases of serous meningitis are presented, all occurring in children with active primary pulmonary tuberculosis. In most cases evidence of local extension of the tuberculosis or extension by the hematogenous route occurred simultaneously with the evidence of meningeal irritation.

Three of the cases presented are well, eleven to fifteen years later. Four died without further evidence of meningeal involvement, four to thirty-two months after recovery from serous meningitis, and 2 of these cases presented pathological evidence of healed nonspecific meningitis.

Signs of meningeal irritation persisted till death in 4 cases and in 3 of these caseous cerebral tuberculomata but no pathological evidence of meningitis were found.

One case of serous meningitis was followed by a brief remission of symptoms and then death from tuberculous meningitis.

SUMARIO

Meningitis Tuberculosa en el Niño con Referencia Particular a la Forma Serosa:
2ª Parte. *Meningitis Tubérculo-Serosa*

Existe un cuadro clínico de meningismo que no es raro en los niños que padecen de tuberculosis primaria activa, y el cual hay que diferenciar de la meningitis tuberculosa.

Por el examen clínico aislado tal vez sea imposible distinguir una meningitis tuberculosa caseosa, de una serosa, en el primer período de la enfermedad.

El examen del líquido cefalorraquídeo ofrece el mejor medio para el diagnóstico diferencial. En la meningitis serosa puede haber hipertensión e hiperglobulia, pero el contenido químico del líquido permanece normal. El hallazgo de algunos bacilos acidorresistentes no resulta incompatible con el diagnóstico de meningitis serosa.

Preséntanse 12 casos de meningitis serosa, todos ellos en niños con tuberculosis pulmonar primaria activa. En la mayoría aparecieron signos de difusión local de la tuberculosis o de difusión por vía hemática simultáneamente con los signos de meningismo.

Tres de los enfermos estudiados se hallan bien, de 11 a 15 años después.

Cuatro murieron sin más signos de invasión meníngea, de 4 a 32 meses después de reponerse de la meningitis serosa, y en 2 de ellos había signos patológicos de meningitis inespecífica curada.

En 4 casos los signos de meningismo persistieron hasta la muerte, y en 3 de ellos encontráronse tuberculomas cerebrales caseosos, pero sin signos patológicos de meningitis.

En 1 caso de meningitis serosa una breve remisión de los síntomas fué seguida de la muerte por meningitis tuberculosa.

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MINIMAL TUBERCULOSIS¹

The Prognosis and Clinical Significance of a Sanatorium Treated Group
I. D. BOBROWITZ,² ALLAN HURST³ AND MARGARET MARTIN⁴

The purpose of this study was to determine the significance of the minimal tuberculous pulmonary lesion, a problem which is of great and increasing importance. The need to diagnose pulmonary tuberculosis in the minimal stage has been met in great measure by the utilization of routine and mass chest X-ray surveys. In these surveys, used for Selective Service applicants and in industrial, hospital and special and general population groups, about 70 per cent of the tuberculosis found was in the minimal stage and of the reinfection type.

Once discovered, the evaluation of the minimal case has been a most perplexing question. No criteria have been established by which one can prognosticate the behavior of the lesion or determine the most desirable mode of treatment. Many authors have emphasized the difficulties present in attempting to differentiate the minimal lesion that will remain stable from the infiltration that will develop progressive disease. The problem is increased by the lack of accurate knowledge regarding the age and evolutionary stage of the lesion when found. Laboratory findings have been of little help in evaluating the prognosis. Because of these uncertainties, recommendations for these patients concerning limitations or modifications of their daily routine, the frequency of periodic roentgenograms and the need of bed-rest have shown wide variations. The decision as to treatment has been especially difficult in the asymptomatic case with negative sputum. Mistakes in supervision and needless removal of persons from their jobs create serious economic and social problems. There has also been considerable difference of opinion regarding the use of collapse therapy in minimal tuberculosis. Some writers advocate collapse measures without delay, but many others advise strict bed-rest first, with active therapy only for those who fail to control the lesion with rest.

This is a review of all patients with minimal tuberculosis admitted to the Municipal Sanatorium at Otisville, New York in 1938 and 1939. These patients were admitted at variable periods after the diagnosis. The basis for inclusion in the study was the interpretation of the initial film taken the day after admission. Only patients with minimal tuberculosis according to the classification of the National Tuberculosis Association and with the characteristic roentgenological picture of pulmonary tuberculosis of the reinfection type were

¹ From the Municipal Sanatorium, Otisville, New York (one of the institutions of the Department of Hospitals of the City of New York), and the Bureau of Tuberculosis, New York City Department of Health.

² Medical Superintendent, Municipal Sanatorium, Otisville, New York.

³ Formerly Supervisor of Clinics, Bureau of Tuberculosis, New York City Department of Health, and now Medical Director, National Jewish Hospital, Denver, Colorado.

⁴ Formerly Consulting Statistician, Bureau of Records and Statistics, New York City Department of Health, and now in the Department of Preventive Medicine and Public Health, Vanderbilt University, Nashville, Tennessee.

acceptable. These cases were further subdivided into four groups, according to the size of the infiltrations, as will be explained later on.

All of the Sanatorium X-ray films were reviewed and described, and the details of the patients' progress (clinical, laboratory) in the institution were recorded. This same type of analysis was continued during the follow-up period and X-ray films and medical records were obtained from the clinic, hospital or private physician that had furnished treatment for the patients. All of the X-ray data were obtained from actual inspection of the roentgenograms and not from the reports alone. All of the Sanatorium and outside X-ray films were read jointly by Doctors Bobrowitz and Hurst.

In this study an attempt has been made to relate the roentgen, clinical and laboratory findings in a series of cases at the time of admission to the Sanatorium, to the behavior of the lesion and the risk of progression during a long follow-up period. Thus we hoped to find the factors or criteria by which the clinical significance and prognosis of minimal tuberculosis could be judged. Tests for statistical significance were applied to all of the differences discussed in this paper.

There were 256 cases with minimal tuberculosis admitted during 1938 and 1939. However, only those cases with at least six months' continuous observation after admission to the Sanatorium were included in the analysis. Thirty-six cases which did not meet this criterion were omitted. The 36 cases which were excluded did not vary significantly from the remaining 220 cases which formed the basis for the following study in regard to sex, color, age and character of lesion on entrance.

There were 145 white patients and 75 non-white. Included in the non-white group were 44 Negroes, 26 Porto Ricans and 5 Chinese. Because the numbers in each of the non-white groups were small, all of them were grouped together in the statistical analysis, even though there may have been differences in outcome among them. Such differences would be difficult to detect because of the small number of cases.

There were 103 patients under 25 years, and 117, 25 years and over. The age classification was based on these two main groups in order to determine the behavior of the adolescent and young adults as differentiated from the older age groups. Because of the paucity of numbers it was not considered practical to further subdivide the patients in smaller age groups.

The total group included 127 females (58 per cent) and 93 males (42 per cent). Since little difference between the sexes as regards progression was observed (the cumulative progression rate at the end of five years for males was 40 per cent and for females 43 per cent) and as the number of cases in each group was already small, the cases were not subdivided according to sex. The distributions for each sex by color, character of lesion and period of observation did not vary significantly.

In grouping the patients by type of lesion, we utilized the excellent definitions for the roentgenological character of the infiltration described by Reisner and Downes (1):

"Exudative: Roentgenologically, the density usually shows rather ill-defined borders, occasionally it may be well circumscribed; it is 'soft' in appearance, either round or irregular in shape. The size is variable, usually ranging from one to two or three centimeters in diameter. The individual lesion may represent either a single focus or it may be composed of several smaller confluent densities. The intensity of the shadow depends on the size of the lesion, it may be either homogeneous or flocculent in appearance.

"Productive and fibrotic: From the roentgenological appearance a distinction may be made between two main forms, namely: (a) discrete nodular densities, usually multiple, of small size, showing well defined borders, 'hard' in appearance, either round or irregular in shape; (b) strand-like or linear densities, sharply outlined, often irregular in shape and distribution. The majority of the cases included in this category present a combination of form 'a' and 'b'.

"Exudative-productive: This form may be regarded as an intermediate group between the two preceding types, the roentgenological findings presenting a combination of the features of both the exudative and productive-fibrotic elements in varying proportions.

"Fibro-calcific form: Roentgenologically, the changes consist of sharply defined nodular densities, showing either round or irregular borders. The nodules are usually multiple; their distribution is scattered; they are generally of small size, measuring several millimeters in diameter, only rarely exceeding one centimeter. The intensity of the shadows is of a type usually interpreted as characteristic of calcium deposition. Such findings often occur in combination with changes indicative of strand-like and linear fibrosis."

Included in our series were 2 exudative cases; 64 exudative-productive; 141 productive-fibrotic; 13 fibro-calcific. As these figures show, there is some preferential selection of the patients admitted to the Sanatorium. Cases that are very ill (acute exudative) and those obviously stable (fibro-calcific) are not often sent to the institution. Thus, there was not an equal distribution of cases by type of infiltration, and most of the lesions were mixed ones, either exudative-productive or productive-fibrotic. Because of the small numbers involved, all lesions with a soft element (group 1, exudative, and group 2, exudative-productive) were grouped together for purposes of analysis, and compared with those productive or calcific (group 3, productive-fibrotic, and group 4, fibro-calcific).

The roentgen behavior of the lesion on serial observation was recorded as follows: (a) stable: unchanged roentgen appearance; (b) retrogression: absorption of exudative areas, increase in fibrosis or calcification; (c) progression: any increase in extent of lesion or cavity formation. Progression was determined only on the basis of roentgen findings.

The total continuous observation period for the 220 patients in this study is given in table 1. Some of these patients were observed for longer periods but data obtained after a lapse of more than six months were not included and the patient was dropped for consideration at this point.

Thus, 43 per cent of the patients were followed up for three years or less, and 57 per cent observed from four to seven years (38 per cent for four and five years and 19 per cent for more than five years).

The distribution of the cases by age, color and type of lesion is shown in table 2.

Of the entire series 66 per cent were white and 34 per cent non-white, and 47 per cent were under 25 years of age and 53 per cent were over 25. Among the white patients the numbers below and above 25 years were practically

TABLE 1
Total period of continuous observation

YEARS	NUMBER OF PATIENTS	PER CENT
1	48	21.8
2	23	10.5
3	24	10.9
4	27	12.3
5	57	25.9
6	34	15.5
7	7	3.2

TABLE 2
Distribution of cases according to age, color and type of lesion

	TOTAL	GROUPS 1 AND 2	GROUPS 3 AND 4
Total.....	220	66	154
White.....	145	48	97
Under 25 years.....	74	29	45
25 years and over.....	71	19	52
Non-White.....	75	18	57
Under 25 years.....	29	10	19
25 years and over.....	46	8	38

equal. The non-white patients showed a preponderance in the older ages with 39 per cent under and 61 per cent over 25 years.

Of the total of 220 patients, 66, or 30 per cent, had lesions classified in groups 1 and 2 (exudative or exudative-productive), and 154, or 70 per cent, were in groups 3 and 4 (productive-fibrotic or fibro-calcific). The proportion for the different types of lesions in the white individuals was 33 per cent for groups 1 and 2, compared with 67 per cent for groups 3 and 4. There was a preponderance of productive and fibro-calcific lesions in the non-white patients, for only 24 per cent were in groups 1 and 2, and 76 per cent in groups 3 and 4.

For the entire group of 220 cases, and making no allowance for varying periods of observation, 147 had remained stable or retrogressed, and 73 had progressed.

Table 3 indicates the progression rates at yearly intervals during a five-year period. The observation was limited to the first five years, as beyond that period few cases were observed and the rate of progression was extremely low.

The cumulative percentage shows a progression rate of 42 per cent for the entire group of 220 cases for a total observation period of five years. In other words, if all of the 220 cases had been followed up for five years and if progression rates had been the same as those observed in each year, 42 per cent would have shown some progression by the end of five years.

Most of the progressions occurred during the first two years of follow-up observation; more cases progressed in the second year (21 per cent) than in any other period. The differences in rates of progression in the first and second years, however, were not significant. The proportion of cases that progressed during the third, fourth and fifth years after remaining stable or retrogressive for two years was significantly smaller than the proportion that progressed during the first two years. Actually about 13 per cent of the cases were in

TABLE 3
Percentage of cases showing progression during five years after admission to Sanatorium

YEARS AFTER ADMISSION TO SANATORIUM	PERSON-YEARS OF OBSERVATION	NUMBER WITH PROGRESSION*	PERCENTAGE WITH PROGRESSION	CUMULATIVE PER- CENTAGE WITH PROGRESSION IN PAST AND SPECIFIED YEARS
First year.....	204.5	32	15.6	15.6
Second year.....	140.0	30	21.4	33.7
Third year.....	90.3	7	7.7	38.8
Fourth year.....	64.0	2	3.1	40.7
Fifth year.....	39.5	1	2.5	42.2

* One case which progressed after five years is not included.
(See appendix for method used in computing person-years of observation and cumulative percentages.)

this category. The incidence of progression was of some importance in the third year (8 per cent) but was of little significance beyond that period.

The Sanatorium treatment of the patients was based upon the usual criteria for tuberculous activity, that is, symptoms, bacteriological findings and the roentgenological appearance of the lesion. Patients who, on admission or during Sanatorium observation, had constitutional symptoms, a positive sputum or exudative elements in the roentgenogram, or instability of the infiltration, would be placed on complete bed-rest (infirmary care). Patients would be transferred from infirmary to semi-infirmary care when they had a negative sputum, were not toxic and had no soft infiltration. (Patients with healing changes, such as increase in fibrosis, might be in the semi-infirmary.) When X-ray stability had been achieved, the patients would become ambulatory. As the patient's physical condition improved, the daily work tolerance would be increased gradually.

The observation period includes the time in the Sanatorium and after dis-

charge, and is figured from the date of the first X-ray film. The average Sanatorium stay for the entire group of 220 patients was six months and only a few patients (including 4 of the 73 that progressed) stayed longer than a year. Actually, therefore, the second year of observation represented for most patients a period shortly after discharge from the Sanatorium. That the progression rate is highest in the second year may be connected with this fact. Of the 73 patients who progressed, only 13 did so while still in the Sanatorium (all of these were during the first year of observation), while 60 progressed after departure from the institution.

The Sanatorium treatment these patients had is tabulated in table 3A.

The 60 patients who progressed after leaving the Sanatorium and the 147 patients who showed no progression did not differ significantly in the type of treatment they received while in the institution. The 13 patients who progressed in the Sanatorium differ significantly from the other two groups, since they show a higher proportion of time in the infirmary and semi-infirmary. Of these 13 cases, 10 were exudative or exudative-productive on entrance which

TABLE 3A

Treatment and duration of stay in Sanatorium, according to progression

	TOTAL NUMBER	AVERAGE NUMBER OF MONTHS TREATMENT IN SANATORIUM		
		Infirmary	Semi-Infirmary	Ambulatory
Progressed while in Sanatorium.....	13	2.0	2.6	6.8
Progressed after leaving Sanatorium..	60	.2	.5	5.0
Did not progress.....	147	.2	.6	4.7

would, no doubt, account for the infirmary care. In only 3 of the 13 was there a change from an ambulatory status to infirmary care.

These figures and the high incidence of progressions during the first two years of follow-up observation suggest the following thoughts in relation to treatment. The period of Sanatorium care might be lengthened and the standards by which patients are now discharged modified to require longer observation. In this respect, stricter criteria concerning the classification of the clinical status of arrest might be advisable. It should be emphasized that intensive, prolonged post-sanatorium care is most important. The ultimate outcome in a minimal case can be favorably or unfavorably influenced by the type of follow-up observation and post-sanatorium living conditions. One must guard against relaxation of close medical supervision, an unregulated daily work tolerance, excessive social activities and economic and environmental deficiencies.

The relation of the progression of the tuberculosis to the age and color of the patients and character of the lesion is indicated in table 4.

The cumulative percentage of progression at the end of five years showed a definite relationship to age, the adjusted rates being 57 per cent for those under 25 years, and 37 per cent for those 25 years and over. The greater risk of

progression in younger patients with minimal tuberculosis is therefore clearly indicated.

There was very little variation between the white and non-white patients with respect to progression. There were very slight differences observed in favor of the white patients under 25 and in favor of the non-white patients over 25, but because of the small number of cases these findings were not statistically significant. In regard to risk of progression, therefore, the age of the patient appears to be more important than the color.

The adjusted five-year cumulative rates of progression were 55 per cent for the exudative and exudative-productive lesions (groups 1 and 2) and 39 per cent for the productive-fibrotic and fibro-calcific lesions (groups 3 and 4). From the standpoint of the total number of patients, therefore, the prognosis is better for the productive and calcific lesions, but the difference in the risk of progression

TABLE 4
Cumulative progression rates at the end of five years, adjusted for color, age and character of lesion

	TOTAL	GROUPS 1 AND 2	GROUPS 3 AND 4
Total.....	46.9	51.8	39.0
Under 25 years.....	56.6	55.7	57.6
25 years and over.....	37.2	53.9	20.4
White.....	48.5	55.0	41.9
Under 25 years.....	56.1	53.0*	59.2*
25 years and over.....	40.8	57.0*	24.6*
Non-white.....	45.3	54.5	36.0
Under 25 years.....	57.1	58.3*	55.9*
25 years and over.....	33.5	50.8*	16.2*

* These rates are actual age, color and character specific rates.
All others are adjusted on basis of an equal number of cases in each color, age and character group.

between exudative and exudative-productive lesions and the productive and fibro-calcific lesions is due principally to the lower rate of progression for groups 3 and 4 in patients over 25. Under 25, there was very little difference in progression between the various types of lesions. Over 25 years of age there was a greater progression rate in patients with exudative and exudative-productive lesions than in those with productive-fibrotic or fibro-calcific lesions. This relationship of progression to age and type of lesion was the same in both the white and non-white patients.

The percentage of cases that progressed was lower in patients over 25 for both groups of lesions among both white and non-white, but the age difference was much more marked among cases with productive-fibrotic and fibro-calcific lesions than among cases with exudative and exudative-productive lesions. Among the latter, the difference in progression rates between the age group over and under 25 was not statistically significant.

Chart 1 shows the cumulative percentage of progression at the end of each year adjusted for color by age and type of lesion.

Chart 1 demonstrates that the cumulative progression rates adjusted for color were lower in patients over 25 with productive-fibrotic and fibro-calcific

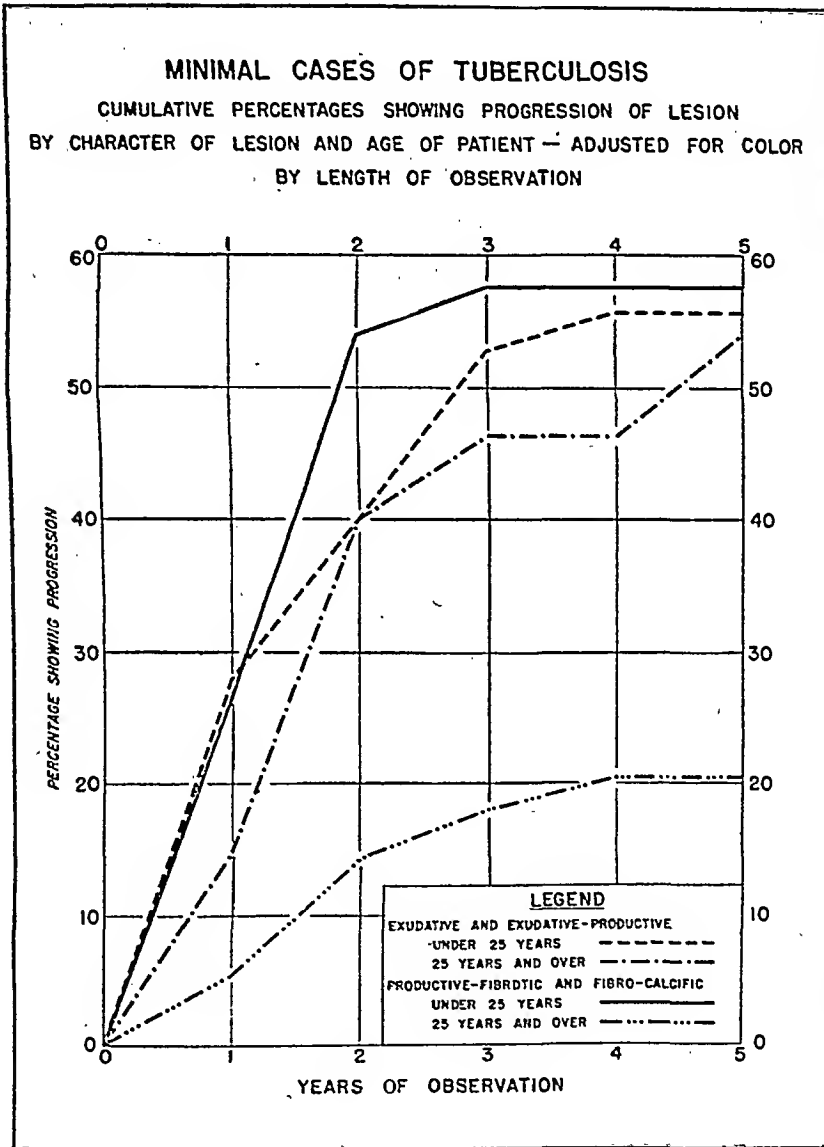


CHART 1

lesions that in the other three groups, which showed much higher and similar rates.

The relationship of age and type of lesion to the risk of progression has been clearly indicated. Whereas the adjusted cumulative five-year progression rate

for all the patients was 47 per cent, the adjusted cumulative progression rate under 25 years was 57 per cent for all types of lesions, and a similar progression rate (54 per cent) was found in patients over 25 with exudative and exudative-productive lesions. There is a lower risk of progression (20 per cent) in patients over 25, but only in those with productive-fibrotic and fibro-calcific lesions. At the time of leaving the Sanatorium, 45 per cent of the exudative and exudative-productive cases had become productive-fibrotic and fibro-calcific, and 1 per cent had changed from productive-fibrotic and fibro-calcific to exudative-productive. The totals for the groups at entrance and on departure were as follows:

	On Entrance	On Departure
Group 1—Exudative.....	2	0
Group 2—Exudative-productive.....	64	38
Group 3—Productive-fibrotic.....	141	168
Group 4—Fibro-calcific.....	13	14

Thus, on departure, groups 1 and 2 comprise 17 per cent of the total, and groups 3 and 4, 83 per cent. Seventy-three patients of the 220 progressed and the first change in these patients revealed the following:

- In 39 cases the first progression observed did not involve a change in stage.
- In 18 cases the first progression observed was to a moderately advanced stage with cavity formation.
- In 12 cases the first progression observed was to a moderately advanced stage with formation.
- In 4 cases the first progression observed was to a far advanced stage with cavity formation.

Therefore, among these 73 patients the initial change included cavitation in 16. Of the 57 remaining cases, 21 eventually developed cavities so that, of the total 220 patients, 37, or 17 per cent, developed cavities. The subsequent history, in so far as it is known, of the 73 cases that progressed, has been outlined in table 5. There is separate grouping of those that progressed during the first year after entry into the study and those that progressed later after stability during the first year.

Among these 73 cases, 20, or 27 per cent, had no further progression during the period of observation after the initial change and the lesion appeared stable roentgenologically. The cases that progressed during their first year of observation appear more unstable than those that progressed later, as only 4 of the 20 without further progression were in the first-year group. However, no definite conclusion can be drawn from this because of the short period of observation for some of the cases. Twenty-four of the patients continued to progress in the year following the initial progression. Eight patients were stable in the year following the first progression before they progressed again and one patient was stable for two years before the second progression. Eight patients received pneumothorax after the first progression. Among the cases that continued to progress (at some other time after the first year following progression) 12 other patients received pneumothorax. Thus, 20 of the 220 patients, or 9 per cent of

the total group, received pneumothorax therapy. Of the 37 cases with cavities, 16 had pneumothorax; 4 patients without cavities also received pneumothorax. Eight patients died from tuberculosis after progressing and one patient died from tuberculosis later, after being stable during the period of observation. There were, in addition, 2 nontuberculous deaths (one among the 147 stable cases and the other a case which became stable after the first progression). In 4 cases there was no further observation after the first progression.

According to the mortality rates prevailing in New York City during the period from 1939 to 1941, the number of deaths for the total period of observation from causes other than tuberculosis, to be expected in a group of the same

TABLE 5
Subsequent course of the 75 patients who progressed

	CASES THAT PROGRESSED DURING FIRST YEAR	CASES STABLE DURING FIRST YEAR AND PROGRESSED LATER
No further progression during the period of observation.....	4	16
Continued to progress in year following progression.....	11	13
Stable during year following progression and then progressed again.....	3	5
Stable during two years following progression and then progressed again.....	0	1
Received pneumothorax during year following progression.....	6	2
Died from tuberculosis (not included in previous groups).....	5	3
No further observation after progression.....	3	1
	32	41

age, sex and color distribution, is 2.2. This is not significantly different from the observed number of deaths of 2. The number of deaths from tuberculosis to be expected, based on New York City tuberculosis age, color and sex specific death rates from 1939 to 1941, is 0.7. This is significantly different from the observed total of 9 in the study group of 220 cases.

The behavior of the lesion and the risk of progression in relation to various roentgenological, clinical and laboratory findings was also studied. The cases were grouped according to the location of the lesion on admission to the Sanatorium, depending upon whether the infiltration was purely apical or not and whether one or both lungs were involved. Of the 220 patients, 55 (25 per cent) had lesions in the apex and 165 (75 per cent) had infiltrations in locations other than the apex; and there were 170 unilateral and 50 bilateral cases. The location of the lesion was related to the character of the infiltration and the age of the patients. Bilateral lesions were more frequent in patients over 25 years than in those under 25. Subapical lesions were more often exudative or exudative-productive than apical (33 per cent compared to 13 per cent), and unilateral lesions were more often of this character than bilateral (34 per cent

compared to 16 per cent). There was no relation between the location of the lesion (apical or subapical, unilateral or bilateral) and the incidence of progression. The distributions for each type of infiltration by color, sex and age did not vary significantly.

As explained above, the patients were subdivided into four groups according to the size of their lesions. The first group comprised those whose lesion was one-fourth of the maximal extent of minimal disease, the second group those with one-half, the third group with three-quarters, and the fourth group those with lesions equal to the maximum anatomical limits of the minimal lesion, as defined by the National Tuberculosis Association as follows: "equivalent of the volume of lung tissue which lies above the second chondrosternal junction and the spine of the fourth or body of the fifth thoracic vertebra on one side." It is not always simple to classify a case as minimal according to the N.T.A. criteria. The lung volume in the apical part of the chest will depend on the closeness of the ribs, how much of the apex is seen and whether or not one arbitrarily chooses the limits of the upper, lower, or mid portion of the second anterior rib. Some may assume that a minimal lesion is that amount of disease which can fit into two full interspaces without crowding. Because of the many gradations in the amount of infiltration included in a minimal case, it was decided to observe what possible influence the extent of the lesion might have upon the prognosis. The percentages of the 220 cases falling into each one of these four groups were 7 per cent, 37 per cent, 29 per cent and 27 per cent, respectively. The incidence of progression was found to be unrelated to the extent of the lesion within the minimal classification. The distributions for extent by color, age, sex and character of infiltration did not vary significantly.

A study was made of the relationship between white cell count, percentage of lymphocytes and sedimentation rate on the first examination on admission to the Sanatorium and the age, color and sex of the patients, character of the infiltration and incidence of progression. The classification used for the white cell count was above or below 8,000; for the sedimentation rate (Cutler method), above or below 10 mm. in one hour; and for lymphocytes, above or below 35 per cent. There was no apparent relationship between the total white cell count, sedimentation rate and percentage of lymphocytes and the age, sex, color or character of the lesion, except that the sedimentation rate was significantly higher for non-white patients than for white, and for females in both white and non-white groups than for males. The behavior of the lesion or incidence of progression was not related to the white cell count or sedimentation rate. However, the patients with less than 35 per cent lymphocytes progressed more often (five-year-cumulative progression rate of 49 per cent) than those with 35 per cent or more lymphocytes (five-year-cumulative progression rate of 31 per cent); and this difference is significant.

The sputum status at time of entrance to the study was based on the sputum findings (sputum or gastric concentrates or cultures) during the first month in the Sanatorium. Since the routine use of gastric cultures was started in 1939, the figures obtained do not show accurately all the bacteriologically positive cases. The number we found positive is much lower than that in other in-

stitutions where the repeated use of cultures and guinea pig inoculations of sputum and gastric contents has disclosed bacilli in 70 per cent of active minimal cases. It may be that the difference in progression between our positive and negative cases would have been greater, had we utilized a more exhaustive sputum procedure. The sputum findings were not related to the color, sex, age of the patients or character of infiltration, but were significantly associated with the outcome.

At the time of entrance to the study, in 29 patients tubercle bacilli were found in either sputum or gastric concentrates or cultures. Of these 29 cases, the cumulative progression rate at the end of five years was 64 per cent, compared with 39 per cent progression in patients in whom tubercle bacilli were not demonstrated. This difference is significant. Twenty-six patients negative at entrance to the study were positive at a later date. The cumulative progression rate for these patients at the end of five years was 67 per cent, not significantly different from those positive at entrance. Of those 26 patients who became positive after entrance, 6 showed progression at time of change in sputum, 4 showed progression before change in sputum, 4 showed progression after change in sputum and 12 did not progress.

Fifty-five patients, or 25 per cent, were positive at some time and 165 patients were negative throughout. The patients with a positive sputum at some time or other during the period of observation had a much higher cumulative progression rate at the end of five years (65 per cent) than those with a negative sputum throughout (37 per cent). This shows a highly significant relation between positive sputum and risk of progression.

Of the entire 220 cases, 146, or 66 per cent, had one or more symptoms, whereas 74, or 34 per cent, had no complaints. Actually, more patients had symptoms, as only the six most common complaints were tabulated. These symptoms and the number of times each of them were reported follows: cough or expectoration or both (115); chest pain (45); weakness (27); weight loss (14); hemoptysis (8); and night sweats (6). The distributions of those with or without symptoms did not vary significantly by sex, color or type of lesion. However, in the age groups 25 years and over, 79 per cent reported symptoms which was significantly greater than the percentage of those under 25 years reporting symptoms (51 per cent). No significant difference was found in patients with and without symptoms with respect to progression.

COMMENTS

We found that the age of the patients and the character of infiltration, particularly the former, were related significantly to the risk of progression. Reisner and Downes (1) in a study of 469 minimal cases concluded that the character of the lesion was the most important factor in relation to outcome. Their patients with exudative and exudative-productive lesions showed a great tendency to progression, whereas productive-fibrotic and fibro-calcific lesions were characteristically stable. Our material is different as the patients were sanatorium cases; whereas Reisner had an ambulatory clinic group. In our series of 66 exudative and exudative-productive cases only 2 were exudative, while

in Reisner's group of 220 exudative and exudative-productive cases, 140 were exudative. Similar differences occurred in the productive-fibrotic and fibro-calcific group. In our series of 154 such cases, 13 were fibro-calcific, whereas in Reisner's group of 249, 81 were fibro-calcific. The difference in our results could be related to these variations.

Stein and Israel (2) have emphasized that sanatorium patients with minimal lesions are a selected group not comparable to other patients with minimal disease treated in clinics. They state that many clinic patients have a greater proportion of progressive lesions.

The progression rate noted in our series clearly indicates that minimal tuberculosis is not invariably a benign condition. The mere fact that the tuberculosis has been discovered in a minimal stage does not carry with it the assurance that an early and lasting cure will result. The seriousness of minimal tuberculosis is reflected by the risk of progression; but the incidence of progression in itself does not present a complete picture of the prognosis of the lesion, for the ultimate behavior of the infiltration and the final outcome of the case are also important.

Our progression rate includes every roentgenological change, no matter how slight. Actually, of the 73 cases that progressed, in 39, or over half, there was no change in the stage of the lesion at the first progression, whereas 34 were already in the moderately or far advanced stage when progression was noted. Eventually, however, 37, or 17 per cent, of the total 220 cases developed cavities. Nine per cent of the total group received pneumothorax (including 16 patients with cavities) and 9 patients, or 4 per cent, died from tuberculosis. On the other hand, some tendency of the cases to become stable is indicated by the 27 per cent whose lesions, after the initial progression, remained stable during the rest of the period of observation. This shows that our group of minimal cases did not have as bad a prognosis as the incidence of progression itself may have indicated.

We have noted that the incidence of progression is greatest during the second year and that an appreciable risk persists until after the third year. It should be emphasized that careful, close and prolonged observation is most essential to attend properly to a minimal case. It is hazardous to predict the outcome or significance of the minimal lesions on the basis of one film alone.

As regards the interpretation of the X-ray films, there are several points of importance. The location of the lesion and the radiographic technique may create difficulties. The infiltration may be partially or almost completely obscured by the first rib, clavicle or other ribs; apical, lordotic or oblique views would be necessary to visualize clearly the lesion. Technical factors are important, for the lesion may be made to look denser and smaller, or larger and softer, by variations in exposure and differences in the developing process. It is not always easy to classify a pulmonary lesion in pathological terms by reading a roentgenogram, especially on the basis of a single film. Interpretation is particularly difficult when the lesions, instead of being few and scattered and clearly definable, are many, diffuse, mixed in type and conglomerate. Of course, the personal equation is also of much importance. This was evident,

as in a good number of films, especially in the large group of mixed exudative-productive and productive-fibrotic lesions, there was not always immediate agreement as to the character of the infiltration and differences of opinion were settled only after discussion.

CONCLUSIONS

This is a study of 220 sanatorium patients admitted with minimal tuberculosis in 1938 and 1939. Seventy-three of these patients showed evidence of progression. A cumulative five-year progression rate of 42 per cent was found for the entire 220 cases.

The most significant single factor related to the outcome of the minimal lesion was the age of the patient. The risk of progression was definitely greater in patients under 25 years of age. The difference in behavior between the soft lesions and those of a hard nature was influenced not by the character of the lesion alone but also by age. The exudative and exudative-productive lesions had a similar rate of progression in patients under and over 25 years. Productive-fibrotic and fibro-calcific lesions had as high a progression rate as exudative and exudative-productive lesions in patients under 25 and a considerably smaller incidence of progression only in patients over 25. In other words, the favorable tendencies in the behavior of the lesions of productive and calcific nature existed only in the older age groups.

A significant relationship was found in the percentage of lymphocytes with a slightly greater risk of progression in those with less than 35 per cent lymphocytes. The sputum findings were highly significant, for the patients with a positive sputum had a much higher progression rate than those with a negative sputum.

The factors which were unrelated to the incidence of progression were the following: (a) total white count; (b) sedimentation rate; (c) presence or absence of symptoms; (d) location of the lesion; and (e) extent of the infiltration within the minimal classification. There were little differences between the sexes and between the white and non-white patients with respect to progression.

CONCLUSIONES

Tuberculosis Mínima

Abarca este estudio 220 enfermos recibidos en un sanatorio con tuberculosis mínima en 1938 y 1939. Setenta y tres revelaron signos de agravación. Para la serie de 220 casos el índice quinquenal cumulativo de agravación representó 42 por ciento.

El factor aislado más significativo en relación con el desenlace de la lesión mínima fué la edad del enfermo, siendo netamente mayor el riesgo de agravación en los pacientes de más de 25 años. El diferente comportamiento de las lesiones blandas y las duras se vió afectado no sólo por la naturaleza de la lesión sino también por la edad. Las lesiones exudativas y las exudativas-húmedas mostraron un índice semejante de agravación en los enfermos de menos y más de 25 años. Las fibrosas-húmedas y las fibro-calcificadas mostraron un índice tan

alto como las exudativas y las exudativas-húmedas en los de menos de 25 años y considerablemente menor sólo en los de más 25. En otras palabras, sólo en los grupos de mayor edad observóse una tendencia favorable en el comportamiento de las lesiones de índole húmeda y calcificada.

Observóse una relación significativa en el porcentaje de linfocitos, con un riesgo levemente mayor de agravación en los que tenían menos de 35 por ciento de linfocitos. Los hallazgos en el esputo fueron muy significativos, pues los enfermos positivos mostraron un índice de agravación mucho mayor que los negativos.

Los factores que no guardaron relación con la incidencia de la agravación fueron: (a) fórmula leucocitaria total; (b) índice de sedimentación; (c) presencia o ausencia de síntomas; (d) localización de la lesión y (e) extensión de la infiltración, dentro de la clase mínima. Hubo pocas diferencias entre los sexos y entre los enfermos blancos y de color con respecto a agravación.

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APPENDIX

Method of calculating cumulative progression rates

All Cases

COMPLETED HALF-YEARS OF OBSERVATION	CASES AT BEGINNING OF HALF- YEAR	WITHDRAWN		PERSON YEARS OF OBSERVATION	PER CENT PROGRESSION PER YEAR OF OBSERVATION	PER CENT STABLE PER YEAR OF OBSERVATION	CUMULATIVE PERCENTAGE	
		Stable	Progressive				Stable	Progressed
1	2	3	4	5	6	7	8	9
0.5 year	220	31						
1.0 year	189	13	32	204.5	15.6	84.4	84.4	15.6
1.5 years	144	8						
2.0 years	136	13	30	140.0	21.4	78.6	66.3	33.7
2.5 years	93	5						
3.0 years	88	13	7	90.5	7.7	92.3	61.2	38.8
3.5 years	68	8						
4.0 years	60	11	2	64.0	3.1	96.9	59.3	40.7
4.5 years	47	15						
5.0 years	32	17	1	39.5	2.5	97.5	57.8	42.2

Column

- 1 If the last observation occurred in the middle of the year, it was counted as an observation for half of the last year only.
- 2 The number at the beginning of the previous period, less those withdrawn during the previous period, *e.g.*, 144 at beginning of third half year is 189 less 13 stable and 32 progressed.
- 3 Stable cases are withdrawn when observation ended.
- 4 Cases showing progression cease to be a part of the observed group after progression has been noted.
- 5 The number observed for a full year plus one-half the number observed for a half year only, *e.g.*, in first year 189 observed for full year and 31 for a half year— $189 + \frac{31}{2} = 204.5$.
- 6 The number who progressed divided by the person years of observation, *e.g.*, in first year— $32 \text{ progressed} \div 204.5 \text{ person years} = 15.6 \text{ per cent progression}$.
- 7 The percentage which progressed subtracted from 100 per cent, *e.g.*, in first year $100 \text{ per cent} - 15.6 \text{ per cent progression} = 84.4 \text{ per cent stable}$.
- 8 The cumulative percentage stable the preceding year multiplied by the percentage stable in current year, *e.g.*, $78.6 \text{ per cent stable during second year} \times 84.4 \text{ per cent stable at end of first year} = 66.3 \text{ per cent stable at end of second year}$.
- 9 The cumulative percentage stable subtracted from 100 per cent, *e.g.*, at end of second year $100 \text{ per cent} - 66.3 \text{ per cent stable} = 33.7 \text{ per cent progressed}$.

THE MANAGEMENT OF THORACIC WOUNDS^{1,2}

Wm. M. TUTTLE³

Wounds of the chest sustained in battle comprise a significant proportion of injuries so obtained. This is especially true when one considers the numbers of persons whose thoracic wounds are fatal. The history of past wars when compared with modern experience is of interest in this respect, for formerly a high percentage of persons so wounded, who in a living state reached some medical installation, later died. They died mainly from deranged physiology and from sepsis. It might be expected that with the increased knowledge of pulmonary physiology and with one of the several chemotherapeutic agents as adjuncts to better surgery the results in soldiers with thoracic wounds would be better in the recent war.

At the beginning of World War I there were few surgeons whose knowledge of the chest was great. It was a new field of surgery where operative endeavor was accompanied by high morbidity and fatality rates. Experience gained in World War I gave impetus to a search for a better understanding of the principles of physiology and pathology involved. The work of Graham and Bell (1) in this country was notable among those early endeavors. The war, as far as this country was concerned, was soon over and it remained for the investigations of many, during the ensuing years, to gather the knowledge and skill so essential to an adequate understanding of pulmonary surgery.

INCIDENCE OF THORACIC WOUNDS

Prior to the Crimean War (1854-1856) little was known of the incidence of thoracic wounds. During that conflict they appeared to have comprised approximately 7.2 per cent of all wounds which reached a medical installation (2). Throughout the years which were to follow and during which numerous conflicts were fought, the pattern of wounding as it applied to the incidence of thoracic wounds appeared to run closely around this figure. New instruments of war and an increase in the lethality of such instruments do not appear to have altered within the range of error, the incidence of such injuries. Records of thoracic wounding exist from the Crimean War until World War I. The pattern is almost constant, ranging from 6 to 9 per cent. During World War I the incidence of such wounding in American troops was reported to be 2.6 per cent of all wounds. In the British Army the incidence was not unlike that of our Army, being 3.8 per cent of all wounded who reached a medical installation. According to the German and French experience, incidence figures were 6.2 and 9.6 per cent, respec-

¹ From the Surgical Service of the 36th General Hospital.

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³ Lt. Colonel, M.C., A.U.S. Present address: 307 David Whitney Building, Detroit 26, Michigan.

tively. Carter and DeBailey (3) report that the American figure of 2.6 per cent was probably due to the fact that in the final tabulation of injuries, shoulder girdle wounds which not uncommonly injure the lung and chest wall were tabulated as upper extremity wounds. The final report of wounds in World War I revealed shoulder girdle injuries to be uncommonly high.

Early tabulations of wounds incurred in World War II indicate that thoracic wounding comprised approximately 8 per cent of all wounded men who reached a medical installation. The Russians reported at that time a similar incidence in a much larger group of wounded.

Wounds during World War II were produced in the main by small arms fire (bullets) or by high explosive shells (shell fragments). Shrapnel was little used. There can be little doubt from previous experience that bullet wounds are less fatal than an injury sustained as a result of shell fragments. The latter are larger and their contours are more irregular and because of these factors they produce greater chest wall and pulmonary damage. However, once the injury has been sustained the percentage of complications seems to be quite as common in either type of wound. This is borne out by a recent report of my associates and myself (4). In 140 patients in whom decortication of the lung was carried out for organizing hemothorax, approximately 25 per cent had been wounded by small arms fire. Such a percentage follows fairly closely the incidence of small arms fire and high explosive shell wounding.

Thoracic wounds produce certain sequelae which require treatment. It seems best to take them up in the following order:

- 1: Thoraco-abdominal wounds.
- 2: Wounds of the mediastinum.
- 3: Intrathoracic and intrapulmonary foreign bodies.
- 4: Sucking wounds of the chest.
- 5: Tension pneumothorax.
- 6: Hemothorax.
- 7: Empyema

THORACO-ABDOMINAL WOUNDS

Combined thoraco-abdominal wounding constitutes one of the most serious types of injury seen in either war or civilian life. Not only is the patient subjected to the severe shock which accompanies any serious wound but he is further jeopardized by the anoxia which often is a companion of chest wall disruption. Such wounds comprise approximately 10 per cent of thoracic wounds and this figure apparently has been closely the same during the recent war as in World War I. The fatality from such wounds in World War I was roughly 60 per cent. Carter and DeBailey (3) state that such wounding gave a fatality of from 25 to 40 per cent in the recent war. The latter figure was undoubtedly true when the war was new. As experience added further knowledge to things known, this rate fell until it approached, in the last months of the war, a remarkably low figure.

Early in our experience many thoraco-abdominal wounds were treated by a celiotomy and, if needed, a thoracotomy. Such a dual procedure not only made

the patient the recipient of two most formidable operations, but subjected surgical teams to much extra exertion. As time progressed it became evident that such injuries could be approached in most instances more advantageously from the thoracic side.

Left-sided thoraco-abdominal wounds are almost routinely better treated from the thoracic approach. If the diaphragm is perforated and the missile has traversed the abdomen, then the wounded diaphragm can be opened more widely and the abdomen explored. It became a routine matter to repair gastric and intestinal wounds through this approach unless the extensiveness of the abdominal wound made such an approach unwise from the standpoint of adequacy. The spleen which is often injured in this type of wound can be more readily and more easily approached through this method of entrance than through the abdomen. Kidney wounds may be explored and there are numerous instances in which the kidney has been removed. When the large bowel is injured the incision can be enlarged and the bowel exteriorized.

It has been said that right-sided thoraco-abdominal wounds give less immediate difficulty than similar wounds on the left. This is probably true, for left-sided wounds give a high percentage of splenic damage with its severe hemorrhage, and a higher incidence of injury of large and small bowel. This is because the liver which occupies the right subphrenic space is a large and resilient organ which, while it may hemorrhage profusely when wounded, impedes the progress of missiles and thus protects the other abdominal viscera.

Late complications, such as empyema, organizing hemothorax and biliary-pleural fistulae, are certainly much more frequent on the right, as might be expected. There is a considerable tendency for the right diaphragmatic closure to disrupt and give rise to empyema of the pleura.

When the war was old and much had been learned, these things were known. All thoraco-abdominal wounds should be explored, preferably by the transthoracic route. The abdomen should be entered through the diaphragm on the left, unless there is reason to believe that abdominal viscera at great distance from the diaphragm have been injured; in such an event the appropriate abdominal incision should be used. The diaphragm should be repaired with silk or cotton and, if time allows, the closure should be in layers. I do not believe from my experience that it is necessary to repair a diaphragm incised in the course of a trans-thoracic gastrectomy or esophagectomy with such precision, but where wounding is severe and soiling of the field is great, the diaphragm carefully repaired most certainly preserved its integrity better. Fine sutures and the avoidance of strangulation of large areas of tissues, while taking longer, pay well in the final result.

When the wound was on the right, injury to the liver was the most common complication. Hemorrhage from such liver wounds was often great and the need for hemostasis was correspondingly large. However, the majority of such wounds cease to bleed and the use of large packs with their resultant pressure and necrosis upon an already not too secure diaphragmatic suture line may do more harm than good. In our early experience numerous right-sided diaphragmatic

wounds broke down. This was in part due to too large liver packs and in part to failure to drain below the diaphragm. These two errors probably contributed more to the poor results in this group of patients than any other mistake. When the poor outcome from such wounds in World War I is considered the results in this war must be appreciated as excellent. Betts (6) has recently reported 903 thoraco-abdominal wounds treated by the Second Auxiliary Surgical Group during the recent war. The fatality rate in this large group of severe wounds was 27.3 per cent. In a group of 48 patients with similar wounds operated upon by Betts the fatality was 22.9 per cent. Sheffs (7) in a personal group of 55 thoraco-abdominal wounds had a fatality of 16.3 per cent, which is indeed a remarkable series.

The figures of Betts and Sheffs are based on observations made in first priority surgical hospitals. Deaths which occurred later in these groups are not considered in the stated fatality percentages. It is my opinion, based on almost 100 thoraco-abdominal wounds cared for in a thoracic center in the same theatre, that the number of late deaths was exceedingly small and would augment the fatality figures only slightly.

Wylie, Hoffman, Williams and Rose (8), reporting on another aspect of the experience in the treatment of the thoraco-abdominal casualty, state that the fatality rate fell from 36.7 per cent in 1943 to 20 per cent in 1945. Such figures reveal the improvement gained by surgical experience, chemotherapy and adequate blood replacement in the treatment of this type of wound.

MEDIASTINAL WOUNDS

While no direct figures are available, it seems reasonable to assume that a large percentage of such injuries are immediately or almost immediately fatal. However, it is surprising how many reach forward and rear medical installations. It seems that it may be safely said that all non-fatal wounds of the posterior mediastinum should be explored because of the danger of wounding the esophagus and in the upper mediastinum the trachea. Wounds of the anterior mediastinum if not fatal and in which the foreign body is retained and the heart uninjured can be allowed to wait until they reach a rear echelon installation.

There, better localization of the foreign body can be carried out and the operation can be performed at a time when the mediastinal hematoma has absorbed, thus making the foreign body more easily obtainable.

Intracardiac or pericardial foreign bodies are also better removed in a more permanent installation, unless active cardiac bleeding with tamponade makes immediate operation imperative. It is surprising how little disturbance intracardiac or pericardial foreign bodies cause, up at least to a few weeks time. There are instances where intracardial foreign bodies have been retained for as long as a quarter century without trouble. Such instances of long retained foreign bodies are of interest but should not be used as a pattern of treatment. There can be little question but that such missiles should be removed as soon as is reasonably possible.

INTRATHORACIC AND INTRAPULMONARY FOREIGN BODIES

Early in the war there was considerable disagreement whether or not foreign bodies should be removed. There was also disagreement as to the maximum size of foreign bodies which should be allowed to remain. In a study of this question in the Italian Campaign, Tuttle, Langston and Crowley (5) showed that foreign bodies removed soon after wounding gave approximately 30 per cent poor results. When similar missiles were removed three to four weeks after wounding poor results fell to less than 1 per cent.

The reasons for these figures become clear upon consideration. The recently wounded soldier is in the main not a good operative risk and, if it is possible to obtain better results by conservative treatment, such a method of attack is preferable. When the foreign body lies within the lung it is generally surrounded by a hematoma of varying size. This hematoma often makes palpation of the missile difficult if not impossible. If found, its removal often causes considerable lung damage, sometimes with a recurrence of pulmonary bleeding.

If a thoracotomy must be done early and the foreign body is easily available it should be removed, but if it appears that its localization and removal may be a prolonged and hazardous procedure, then it should be left to be removed at a more propitious time.

Hematomata of the lung readily absorb and disappear within one month's time. It became our practice to await absorption of the hematoma before attempting to remove the foreign body. There have been, undoubtedly, instances in which foreign bodies contained within the lung caused suppuration, but in a large experience with intrathoracic wounding I have not seen it to occur.

Certain surgeons have felt that bone fragments driven into the lung by the wounding agent gave rise to suppuration more readily than metallic foreign bodies; I do not believe that this is so and I feel that early thoracotomy for their removal is not indicated. It seems inconceivable that fine or even large spicules of bone could be found within a badly traumatized lung. I have found them most difficult to remove even in patients seen late when the hematoma was gone and the lung had returned to normal.

SUCKING WOUNDS OF THE CHEST

It has long been the policy of first aid men to apply, as soon as the wounded man is found, a tight thoracic dressing to such types of wounds. The wound as a rule is so labeled and, as soon as it is seen by a medical officer, steps are taken to repair the defect, even if the repair is only temporary. In cases with great chest wall damage, thoracotomy becomes a necessity and adequate steps must be taken to repair the defect immediately. It has been my experience that such wounds, carefully repaired with a layer-by-layer repair, do better than those carelessly repaired. Foreign bodies readily accessible during such thoracotomies should be removed, those difficult to localize should be left.

TENSION PNEUMOTHORAX

The treatment of such states resembles closely those in civilian life. Interestingly enough in this war their incidence was relatively small. This was

probably because the chests of most of our soldiers were normal, the abnormal having been screened out by the initial roentgenographic study. Thus, when injury to the lung occurred, the lung collapsed completely and the wound closed. By the same token, subcutaneous emphysema in extreme states was seldom seen. Thus two conditions which for centuries were described and dreaded by military surgeons were seldom seen.

Such wounds were treated by catheter, water-seal-drainage and a thoracotomy was seldom done. When the defect was large and it was impossible to close the pulmonary wound by reëxpansion, thoracotomy was indicated.

HEMOTHORAX

Hemothorax constitutes the commonest complication of thoracic wounding. Most thoracic surgeons had been lulled by civil practice into the thought that it seldom produced serious trouble and that, whether aspirated or not, the end-results were uniformly good. It soon became apparent that this was not so. Hemothoraces clotted, fibrosed, the hemithorax contracted, the lung became encased. The patient so affected became useless as far as military service was concerned, and his physical activity was strictly limited in civilian life, as well. Another group of soldiers with hemothorax developed suppurative pleuritis, either while the intrapleural blood was still liquid or after it had become clotted. The patient with a suppurating clotted hemothorax went on, as a rule, to a chronic empyema. Those whose unclotted hemothoraces suppurred were, as a rule, more fortunate, for drainage of their empyema usually gave good results. The above description applies to those seen early in the war; later, steps were taken to prevent this.

Hemothoraces were aspirated early. There is little evidence that this is a dangerous procedure. Many pulmonary wounds may bleed copiously at first but, once stopped, there is only the occasional instance where they bleed secondarily. Air was not replaced. Where the total hemothorax was fluid the end-result was good.

It was the clotted hemothorax which gave trouble for the problem of dealing with it was not solved. In the middle of 1943, Major Thomas Burford performed a thoracotomy on such a patient and, after clearing the clot from the pleural cavity, the fibrinous peel was removed from the visceral pleura and the freed lung expanded. Such a procedure was a reapplication of an operation first used by Fowler (9) in 1893 and Delorme (10) in 1894. The lung was decorticated.

Langston and Tuttle (11) have recently written on the pathology of the process involved in intrathoracic clotting. Tuttle, Langston and Crowley reported recently 140 patients with infected and uninfected clotted hemothoraces treated by pulmonary decortication. In this group there were no deaths. The series studies included 89 instances of uninfected hemothoraces and 51 patients in whom gross infection was present. Of the total group, 108 were considered good results, in 26 patients the results were considered fair, and in 6 instances the results were poor.

When this group was considered in another phase, namely, their duty status: 6 of the 140 patients returned to full duty, 64 were sent to limited duty within

the theatre, 44 were returned to the Zone of the Interior because of severe intrathoracic wounds, but most of them were well and would require no further surgery. Twenty-three patients could have returned to some form of duty as far as their chests were concerned but were returned to the Zone of the Interior because of other wounds. These figures reveal the salvage of what had been previously considered long-term cases.

Not only did pulmonary decortication allow numerous men to return to some form of duty, but it likewise allowed those returned home eventually to enjoy a normal life, free from pulmonary crippling.

EMPHYEMA

Suppurative pleuritis has for long years been the worry of military surgeons in every land. In each war, empyemata, acute and chronic, have plagued the surgeon who attended them. This recent war was no exception.

Two types of intrapleural suppurative disease occur: (1) those which take place in an unclotted hemothorax and which, for all ordinary purposes, are simple empyemata; and (2) those which occur in a clotted hemothorax and become complicated empyemata. The former are easily treated with good results by open drainage. The latter by such treatment give poor results and generally result in a chronic empyema.

In the group of decortications reported by Tuttle, Langston and Crowley upon 51 patients with infected clotted hemothoraces, there were 25 instances of primary healing of the empyemata. By primary healing was meant that the empyema space was obliterated within ninety-six hours, and that all intrathoracic tubes were removed within seven days. Twenty-three patients following this method of treatment had residual empyema spaces varying in size from 25 to 200 cc., but healed within a few weeks. In 3 patients it appeared that the residual empyema space might be a chronic one and would require further surgery. It seems likely that, had these patients been treated by simple drainage. It when suppuration had finally liquefied the clotted mass, a high percentage would have resulted in chronic empyemata.

The theory of empyema drainage for many years has been the drainage of a localized area of suppuration. It has always been advised to wait until the intrapleural suppuration has localized before drainage be instituted. In the decortication of a suppurating, clotted hemothorax, a new principle has been stated, namely that the pleural space may be entered in the presence of virulent infection, the peel from the encased lung can be removed leaving a normal pleura. Uninfected areas along the mediastinum and in the fissures may be freed and freely bathed in pus, and still the empyema is cured. This is possible only if the pleural space is obliterated by the expanding lung. If expansion is complete the result will be good even in the absence of chemotherapy. Furthermore, in the group of patients previously referred to, there were only two instances of wound infection, even though these wounds had been covered with infected material for from one to several hours. I feel that this further demonstrates that wounds well closed with non-strangulating sutures heal well, even in the presence of infection.

SUMMARY AND CONCLUSIONS

During the recent war thoracic surgery made great progress. New ideas arose, based on old principles newly applied. The results obtained have demonstrated the soundness of our methods of surgical training in this country. Carter and DeBakey (3) have recently stated that the fatality from penetrating wounds of the chest has fallen from almost 90 per cent in the Crimean War to approximately 15 per cent during World War II. The statistics upon which these authors base their conclusions were, in the main, collected before the wide-spread use of penicillin. Sheffs (7) has recently reported 145 perforating and penetrating wounds of the chest with a fatality of slightly over 6 per cent. The sulfonamides were abandoned relatively early and in our series of patients they were not used. It must, therefore, be concluded that the remarkable drop of a fatality figure of almost 90 per cent to 6 per cent is the result of better surgery, adequate blood replacement, the use of penicillin and a more adequate knowledge of respiratory physiology. None of the triumphs of thoracic surgery noted in this communication would have been possible had it not been for the marked advances made in the field of anesthesiology. No thoracic surgical procedure can be done without the aid, advice and great help of an experienced physician in the field of anesthesiology.

SUMARIO Y CONCLUSIONES

El Cuidado de las Heridas Torácicas

Durante la guerra reciente la cirugía torácica realizó grandes adelantos, surgiendo nuevas ideas, basadas en viejos principios aplicados nuevamente. El resultado obtenido demuestra el acierto de los métodos de adiestramiento quirúrgico utilizados en Estados Unidos. Carter y DeBakey han declarado recientemente que la mortalidad debida a las heridas penetrantes del tórax ha descendido de casi 90 por ciento en la Guerra de la Crimea a aproximadamente 15 por ciento durante la II Guerra Mundial. Las estadísticas en que dichos autores basan sus conclusiones fueron compiladas, en conjunto, antes de difundirse el empleo de la penicilina. Sheffs ha repasado hace poco 145 heridas perforadas y penetrantes del tórax con una mortalidad de poco más de 6 por ciento. Los sulfonamidos fueron abandonados relativamente pronto y en la serie actual no fueron utilizados. Cabe, pues, deducir que la notable baja de una mortalidad de casi 90 por ciento a 6 por ciento es efecto de una cirugía mejor, reposición adecuada de la sangre, empleo de la penicilina y conocimiento más adecuado de la fisiología respiratoria. No hubiera sido posible obtener ninguno de los triunfos de la cirugía torácica aquí descritos, de no haber sido por los grandes adelantos en la rama de la anestesiología. No puede verificarse ninguna intervención cruenta en el tórax sin el concurso, consejo y gran ayuda de un médico adiestrado en anestesiología.

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THE TUBERCULIN TEST^{1,2}

Its Use, Limitations and Future Possibilities in Diagnosis

HENRY C. SWEANY

The tuberculin reaction has had a long and interesting history. The active agent "tuberculin" was first prepared by Koch and heralded with considerable enthusiasm as a "remedy" for tuberculosis. Instead of a cure, however, it proved to be a powerful poison for many patients. As a result, the "lymph," as the first tuberculin was known, was soon abandoned as a therapeutic agent, except in very small doses. The reaction in the infected host, either human or animal, after a subcutaneous injection, was soon found to be useful for the detection of a tuberculous infection. Because of the damage frequently done by the relatively large subcutaneous doses in human beings, Pirquet (1) in 1907 devised the cutaneous scratch test method and gave the name "allergy" to properties responsible for the tuberculin reaction. One year later Mantoux (2) described the intracutaneous administration. Although many other variations have since been introduced none has been found to be so universally dependable as Mantoux's — not even the recent and frequently useful patch test of Vollmer (3).

Technical improvements in tuberculin testing, however, did not result in an accurate method for diagnosis because facts were discovered soon after the introduction of tuberculin which greatly diminished the value of any diagnostic method based on the tuberculin reaction. The pathological studies of Naegeli (4), Orth (5) and others demonstrated that the majority of people had healed tubercles within their bodies — frequently without active disease. Subsequently Hamburger and Monti (6), Veeder and Johnston (7), Armstrong (8) and others learned from tuberculin surveys that nearly all people over 15 years of age living in the larger centres of population reacted to tuberculin. The obvious conclusion was that a positive tuberculin reaction merely revealed the fact that the individual had once been infected by the tubercle bacillus with the probability that most of the lesions had healed. For this reason the use of the tuberculin reaction became restricted to infants and young children in whom the infections were recent, and generally confined to family circles.

As time passed, tuberculin testing became a preliminary screening device in case-finding surveys, especially in schools and colleges (9, 10, 11, 12, 13, 14, 15). Dozens of studies including tens of thousands of tests were reported. In some instances enthusiastic workers tended to overemphasize the value of the tuberculin reaction. However, certain significant conclusions could be drawn. A positive reaction was proved to be a literal "game trail" of the first significant sign of the tubercle bacillus. Tuberculin testing was found useful in locating tuberculous foci in family circles by following the reactors in school surveys to their homes. In the practice of medicine, especially in pediatrics, it was helpful in diagnosis of obscure conditions; in finding tuberculosis in older age groups in communities where the infection rate is low, and in ruling out nontuberculous pulmonary conditions. Finally, apart from its diagnostic value, it made a significant contribution to the field of public health education by focusing the attention upon tuberculosis.

¹ From the Laboratories of the City of Chicago Municipal Tuberculosis Sanitarium, North Pulaski Road and Bryn Mawr Ave., Chicago, Illinois.

² Read, in part, before the regional meeting of the American College of Physicians at Chicago, October 25, 1944.

Other facts also were brought out by tuberculin testing. In the first place, it became apparent from tuberculin surveys that there was great variation in the incidence of tuberculosis in different parts of the world. For example, Bushnell (16), Borrell (17) and others showed long ago that some primitive people had little tuberculosis, especially in regions remote from civilized countries. More recently, Scheel (18) found in rural districts in Norway about 25 per cent positive reactors by the age of puberty. Hart (19), in studying admissions to a London hospital, found that the infection incidence gradually increased from infancy until 24 years of age when about 90 per cent of admissions were infected. In our country the tuberculosis incidence was found to vary in different communities and was found generally much lower than the earlier studies indicated. Slater (20), in 1924, in a well-to-do farming community in Minnesota found only 10 per cent of tuberculin reactors in high-school children. Harrington and Myers (21) in a similar study found slightly more than 50 per cent reactors by the age of puberty in the city of Minneapolis. Hetherington (22) found in Philadelphia over 75 per cent reactors in a comparable group. The variation was also present in other countries.

Tuberculin surveys demonstrated a decline in the infection rate of tuberculosis. Chadwick and Zacks (23) repeated tuberculin testing in Massachusetts nine years after Armstrong's work (8) and found that the incidence of infection was 24 per cent less than it was in Armstrong's time. Chadwick and Pope (24) reported half the number of reactors in Massachusetts school children in 1939 that were found in 1924. Thus the conclusion may be drawn from the various tuberculin studies that the incidence of tuberculous infection varies considerably from place to place and is decreasing in the communities where control measures prevail. It is also obvious that there must be a gradual increase in the number of uninfected people in the older age groups and that the tuberculin reaction as a diagnostic agent should increase in usefulness with the passing of time.

Finally, during the few decades since tuberculin has been in use, several reports have appeared on the quantitative value of tuberculin reactions. Most of these studies were conducted with the purpose of determining a "critical threshold" between active and quiescent disease. Von Ellermann and Erlandsen (25), White, Graham and Van Norman (26) and Pottenger (27) were some of the first workers to advocate the quantitative use of tuberculin in the control of tuberculin treatment of human beings. Usually about 0.01 cc. was applied to a scarification of the arm according to Pirquet's method. The objections to the external application of tuberculin for any quantitative use were obvious, and soon Mantoux's method as used by Römer and Joseph (28) in guinea pigs was modified and substituted for the cutaneous method in human beings. Although Hamman and Wolman (29) and Smith (30) failed to find any satisfactory quantitative use of tuberculin tests, Opie and McPhedran (31) reported a measure of success with the quantitative Mantoux method for diagnosis of pulmonary involvement. They injected 0.1 cc. of three dilutions (0.01, 0.1 and 1 mg.) at two-day intervals beginning with the lowest concentration and measuring the diameter of the reaction in millimeters. They graded the reactions from 10 to 15 mm. as 1 plus; 15 to 25 mm. as 2 plus; 25 mm. or over as 3 plus; if there was a necrosis, it was considered 4 plus. They found that 73.9 per cent of children and young adults giving strong reactions to 0.01 mg. had roentgenological evidence of active tuberculosis and that "grave tuberculous infection increases with the severity of the tuberculin reaction." Hetherington, McPhedran, Landis and Opie (32) continued the study and became the first to use the method successfully for diagnosis. Jadassohn (33) used quantitative tuberculin tests in various forms of skin tuberculosis. They made dilutions from 1:10 up to 1:10,000,000 and found that the higher the bacillary content of lesions and generally the

more extensive the caseation, the more intense was the tuberculin reaction. On the same basis, Sulzberger and Wise (36) divided cases with skin tuberculosis into strong reactors (true tuberculosis) indifferent reactors and negative reactors, in which group they included sarcoid lesions. Because of the fact that skin tuberculosis involves the organ being tested, there is a possibility that the quantitative reaction here may be different from that in other forms of the disease.

Most authors have used a similar method of dilution and application, but there have been differences in methods of reading and in the kind of tuberculin used. Atsatt (37), using a Saranac tuberculin, reported a threshold of activity of 1:7,500 dilution of tuberculin between active and inactive or healed tuberculosis of the bones and joints, obtaining 90 per cent negative results in negative cases and 92 per cent positive results in positive cases. He reported his findings in "six degrees of intensity." Blair and Galland (38), using a New York City Board of Health tuberculin, thought that the threshold was at about 1:25,000 dilution, although they did not notice any difference between the 1:25,000 and 1:100,000 dilution. They read indurated reactions of a 10 mm. diameter or more as positive. It appears from their results that the tuberculin used was much stronger than that used by Atsatt. They claimed a 90 per cent positive diagnosis of tuberculosis in cases reacting to 1:100,000 dilution and a 92 per cent negative finding of tuberculosis in cases failing to react to 1:10,000 dilution. King (39), using a Saranac tuberculin and reading a 10 mm. indurated erythema as positive, reported the "critical threshold" between positive and negative cases to be at the 1:20,000 dilution. His results were also claimed to be about 90 per cent correct. Ayman (40), reading a 10 x 9 mm. reaction as positive, found that a 1:50,000 dilution gave 97 per cent negative results in negative cases and 93 per cent positive results (corrected for moribund cases) in positive cases. Westwater (41) in England, using a single injection of a 1:1,000 dilution and reading on an arbitrary scale the degree of reaction, noted in children who were positive that the severity of the reactions *increased* up to 4 to 5 years of age and then decreased to 10 years of age, while the incidence of active disease *progressively decreased* from birth. Massive disease was prone to have a low sensitivity that continued to decrease as the patients became worse. Small lesions, if recent, were prone to cause severe tuberculin reactions. His precautions against error were particularly good. Hunt (42) compared quantitative tuberculin reactions with roentgenological studies and reported that 94.8 per cent of his series of 45 positive cases of tuberculosis reacted to a 1:100,000 dilution. The patients reacting to a 1:100,000 dilution were considered to have active tuberculosis, while the ones reacting only to a 1:10,000 dilution were considered as latent or healed. Lichtenstein (43) carried out Hart's dilution method on a series of cases in our Sanitarium and observed generally a diminution of the size of the reaction in proportion to the duration and severity of the disease. He thought that the reduction in size of the reaction in progressive disease was due to the liberation of tuberculoprotein because, besides the decrease in reaction in long-standing severe disease, there was an *increase* in the size of the reaction when absorption from the lesion was restricted as in collapse therapy. Similar tendencies in the variation of sensitivity were shown in work done by Appel, Jocz and Willis (44).

In most of the studies on the quantitative tuberculin testing there was a considerable difference in what the respective authors considered the "critical threshold" of activity, but the percentage results for positive and negative diagnoses were generally reported to be over 90 per cent. In addition to the differences in methods and materials, some of the variations in results are no doubt due to differences in the clinical material and in the diagnostic criteria prevalent at the time.

On the basis of the work already done, it would appear that within rather narrow limits a clinical threshold of activity may be demonstrated in certain types of tuberculosis, but the reaction does not always distinguish significant disease from the many infections that never develop into clinical activity. Furthermore, it contributes little or nothing in overwhelming infections, desensitized cases or in the many quiescent infections that still contain living bacilli. Most of the work already reported on quantitative reactions involves cases in which a diagnosis has already been made or is otherwise evident and not on cases where the diagnosis is dependent solely upon the quantitative tuberculin reaction.

In view of the many possibilities of further extension of the use of tuberculin in diagnosis, it seems appropriate to reinvestigate the various aspects of the reaction on various types of clinical material in the hope that a more uniform procedure may be found and that a useful application of a much needed test for clinical activity may ultimately be developed.

MATERIAL

The clinical material for this study represented patients entering our Sanatorium and consisting of all types of chest diseases, over 95 per cent of which is tuberculosis. Approximately two-thirds had sputa positive for tubercle bacilli on admission and hence did not require further confirmation of the diagnosis. The 600 cases not found positive immediately seemed to offer an opportunity, as well as a challenge, for a study of the diagnostic possibilities of the tuberculin reaction.

METHODS

The methods used were essentially those used by Opie and McPhedran (31), Hart (19), Sayé (11) and others including Lichtenstein (43), whose work I carried on after he went into the armed forces. One variation from the method in use was the 0.02 cc. injection (described below) given in the opposite arm to expedite the diagnosis.

Old Tuberculin (Parke, Davis and Company) was used in four dilutions: 1:10 dilution (0.1 cc.: 10 mg.); 1:100 dilution (0.1 cc.: 1.0 mg.); 1:1,000 dilution (0.1 cc.: 0.1 mg.); 1:10,000 dilution (0.1 cc.: 0.01 mg.) tuberculin.

All patients with negative sputum on three concentrations for tubercle bacilli were tested by injecting beneath the epidermis, according to the Mantoux procedure, 0.1 cc. of 1:10,000 dilution (0.01 mg.) in the flexor surface of the one forearm. At the same time, 0.02 cc. of 1:1,000 (0.02 mg.) was injected in a similar manner into the flexor surface of the other forearm. The small dosage of a more concentrated tuberculin seems to act more intensely than the same amount of tuberculin in greater dilution. Its use sometimes obviates an intermediate dosage, helps to prevent necrotic reactions and allows practical results within four days or complete results (rarely necessary) in six days. When reactions were positive on the first test, no further work was necessary. Readings were made after forty-eight hours, the process was repeated giving 0.1 cc. of 1:100 (1.0 mg.) and 0.2 cc. (2.0 mg.) of 1:10 dilution. If still negative, 10 mg. were given.

The method of reading the reaction in the past seems to have been rather varied and uncertain. Some authors (Opie, King and Hunt) consider a reaction of 10 mm. as positive. Ayman measured all sizes from 1 x 1 mm. up but considered 10 x 9 mm. as the lower limit of positive. Blair and Galland consider as positive any palpable induration with erythema. Atsatt used "six degrees of sensitivity" without specifying the lower limit. The

lower limit of a positive reaction in this work was the smallest papule surely distinguishable from the scar of the needle or other reactions due to possible nonspecific factors.

CLINICAL OBSERVATIONS

A grouping of the series into tuberculous, nontuberculous and doubtful cases has been made in table 1.

There was a total of 1,619 (86.4 per cent) patients in whom tubercle bacilli were found and 254 in whom bacilli were never found. Of the former, 1,273 (68.0 per cent) were found immediately and 346 (18.5 per cent) found subsequently. Strong presumption of tuberculosis was found in 118 (6.3 per cent); definite nontuberculous disease was found in 71 (3.8 per cent) and presumptive nontuberculous disease was found in 20 (1.1 per cent). The 45 remaining cases

TABLE 1

Findings on 1,873 admissions to the Chicago Municipal Tuberculosis Sanitarium over a period of 498 days

	TOTAL NUMBER OF CASES WITH TOTAL POSITIVE AND NEGATIVE BACIL- LARY FINDINGS		ULTIMATE DIAGNOSIS	
	Number	Per cent	Number	Per cent
Total Admissions.....	1,873	100		
Tubercle bacilli found.....	1,619	86.44		
On 1 to 3 concentrations on admission.....			1,273	67.97
Gastric lavage (delayed positives).....			346	18.47
Tubercle bacilli not found.....	254	13.56		
Presumptive diagnosis: Tuberculosis.....			118	6.30
Not tuberculosis.....			71	3.79
Presumptive diagnosis: Nontuberculous diseases.....			20	1.07
"Medical impressions" only.....			45	2.40
Total	1,873	100.00	1,873	100.00

(2.4 per cent) were classed as "medical impressions" and are detailed in table 3.

Let it be stated that the certain diagnosis of tuberculosis was made only when tubercle bacilli were demonstrated or specific tuberculous alteration was found. If an absolute diagnosis was not made within four months, the presumptive findings or medical impressions were retained, even if the patient returned later with positive findings. The length of time was an arbitrary one; it was the maximum practical time in which a patient can be kept under observation in a chest hospital.

Of the 346 "delayed positives" most of the diagnoses were made on single gastric lavages. According to Feld (45), repeated gastric lavages usually add about 25 per cent more positive results. If 3 to 10 gastric lavages had been made, it is probable that 50 or more positive cases would have been found. A presumptive diagnosis was therefore made on the 118 patients lacking pathog-

nomonic evidence but in whom tuberculosis was suspected on the basis of X-ray or clinical findings or both.

The failure to find tubercle bacilli after a week's time placed the cases in the group of "diagnostic problems." These cases are dealt with so that the tuberculin findings may shed light on the probable diagnosis. There were 600 of these so-called "problem" cases on which the tuberculin studies have been based. Of that number, 11 cases were not tested with tuberculin because of moribund condition or rapid demise. There was a balance of 589 cases actually tuberculin tested.

Up to the present time—two years after the end of the observation—7 cases have become positive in the presumptive group of the tuberculous cases and 3 certain errors have been found (0.5 per cent) among all negative cases. One error was that of a metastatic pulmonary lesion resembling a tuberculous infiltrate resulting from a primary cancer of the adrenal gland; another was a metastatic chorio-epithelioma producing an infiltrative lesion in the lung; and a third was an abscessed cystic lung with an old healed primary tuberculosis. Since all were young adults who had characteristic X-ray shadows and had strongly positive tuberculin reactions, the suspicion of tuberculosis seemed well founded.

The same plan was used with the nontuberculous diseases; a pathognomonic sign was necessary before an absolute diagnosis was made. There were 71 cases having definite evidence of a nontuberculous disease, while 20 could be given only a presumptive diagnosis.

In table 2 are listed the findings at each dilution of tuberculin. In column 2 are placed the cases with an absolute diagnosis of tuberculosis. A rapid decline in the number of cases occurs from the weaker to the stronger concentrations. The respective figures are 269, 58, 14, 3 and 2 for the five groups. In column 3 are arranged the cases with the presumptive diagnosis of tuberculosis. There are about a third as many cases for each dilution as in the "absolute" group. The total positive cases are given in column 4 and the percentages are given in columns 5, 6 and 7. In columns 8, 9 and 10 are the nontuberculous cases. The absolute diagnosis of nontuberculous disease is in column 8, while the presumptive diagnosis is in column 9. The high figures in the cases negative to the 1:10 dilution (10 mg.) are due to 10 cases with the presumptive diagnosis of sarcoidosis based on the clinical condition, the X-ray appearance and the tuberculin reaction, without anything specific of the disease.

Column 11 presents the ratio of tuberculosis to nontuberculous diseases at each dilution. In the 1:10,000 dilution the probability of any given case having tuberculosis is about 16 to 1; in the 1:1,000 the probability is about 5 to 1; in the 1:100 dilution the chances are about even (1.2 to 1), and in the 1:10 the odds are 3 to 1 in favor of a nontuberculous disease. A negative reaction to a 1:10 dilution is 10 to 1 in favor of a nontuberculous condition. While these percentages have not included the cases with a "medical impression" there is little change when figures of the latter are included.

Positive results in the dilution of 1:100 contribute no diagnostic aid at all. The only help given by this dilution is the suggestion of a previous infection, while the probabilities of tuberculosis in weaker dilutions or a nontuberculous

TABLE 2
Result of tuberculin studies on 600 cases negative for tubercle bacillus on preliminary examination

	NUMBER OF CASES OF TUBERCULOSIS AT EACH DILUTION WITH			TOTAL CASES TUBERCULOSIS				NUMBER OF NONTUBERCULOSIS CASES AT EACH DILUTION WITH			RATIO: TUBERCULOSIS TO NONTUBERCULOSIS	"MEDICAL IMPRESSIONS"	GRAND TOTAL
	Absolute Diagnosis	Presumptive Diagnosis						Absolute Diagnosis	Presumptive Diagnosis	Total			
Tuberculin reactions at dilution of	2	3	4	5	6	7		8	9	10	11	12	13
1													
1:10,000	269	94	363	61.6	78.3	91.0		20	3	23	15.8	13	399
1:1,000	58	20	78	13.2	16.8	73.5		13	3	16	4.9	12	106
1:100	14	4	18	3.0	3.9	47.3		15	0	15	1.2	5	38
1:10	3	0	3	0.5	0.6	15.8		8	2	10	0.3	6	19
1:10 negative	2	0	2	0.3	0.4	7.4		7	12	19	0.1	6	27
Total cases tested	346	118	464							83		42	589
Number of cases not tested										8		3	11
Grand total			464							91		45	600

disease in stronger dilutions increase, respectively, in each direction. The results in the two extremes have much presumptive value in diagnosis, especially the positive reactions to the 1:10,000 dilution and the negative findings at the 1:10 dilution.

The demonstration of definite tuberculosis in positive findings in the 1:1,000, 1:100 and 1:10 dilutions depends, therefore, largely upon a persistent search for the tubercle bacillus rather than on the tuberculin reaction. As pointed out elsewhere, more stomach washings upon admission would probably have found more positive cases or, as we are doing now, obtaining nearly 100 per cent results by bronchial aspiration. It is interesting to note that the bacillary findings were approximately the same in the cases positive in the stronger dilutions of tuberculin (1:1,000 and stronger) and in the 1:10,000 dilution. The latter had 74.1 per cent positive cultures while the former had 76.3 per cent positive cultures. The decrease in tuberculin sensitivity in most of these cases would seem to be due, therefore, more to desensitization or overwhelming disease rather than to an eradication of the infection and healing.

In the active cases positive to the 1:10 dilutions, one (M. K., No. 422) was terminal at the time of the test, and another (L. L., No. 257) had a massive involvement of one lung with only slight clinical symptoms. Although the reaction was atypical at first, bacilli appeared later in the sputum to confirm the diagnosis of tuberculosis. It is possible that this case was a primary infection in a young adult. The third case (A. F., No. 254) had an old quiescent fibroid tuberculosis of twenty years' duration.

In the 12th column of table 2 are the cases with an uncertain diagnosis. By applying the percentages of the 7th column to figures of this column, there should be 12 cases of tuberculosis in the 1:10,000 dilution; 8 in the 1:1,000; 2 in the 1:100 and 1 in the 1:10 group, making a total of 23 cases. The actual number of cases of the "uncertain group" in which the evidence pointed to tuberculosis and to which such a "medical impression" was given was 10 for the 1:10,000 dilution, 5 for the 1:1,000 dilution, 1 for the 1:100 dilution, 4 for the 1:10 dilution, and none for the negative in the 1:10 dilution—a total of 20.

The various "disease impressions" of the 12th column of table 2 are listed in table 3. Since this work was completed, 4 cases with a medical impression of cancer have died and the "impression" was found correct. Another one died but a postmortem examination was not obtained. In 4 with a medical impression of tuberculosis, tubercle bacilli were found and one abscess was operated on by lobectomy. All the positive findings were obtained only after four months' time — too late to permit the inclusion of the cases in the group with positive findings. The other 35 patients (of whom 16 were suspected of having tuberculosis) either went home too soon or had complicated histories of several ailments so that a complete diagnosis could not even be presumed. The cases involved combinations with leuc; abscess; chronic pneumonitis with effusion; sickle cell anemia with general lymphadenopathy, etc. Generally one of the conditions was definite, but there was one or more other complicating conditions which prevented a complete diagnosis before the time limit was passed.

In table 4 the 589 cases of the study were classified as follows: acute to subacute and apparently active tuberculosis; chronic, including fibroid, healed and slightly or totally inactive disease; complicated, including tuberculosis with associated diseases; various nontuberculous diseases and two miscellaneous groups.

The first group was rather ill defined, as it is sometimes difficult to distinguish a slowly progressive subacute type from a chronic type. Most of the chronic fibroid group, however, were clinically quiescent if not inactive or healed. In spite of the uncertainties mentioned, there seemed to be a trend in favor of strong tuberculin reaction in acute disease and a diminution of reaction in the quiescent and healing types. Important nontuberculous diseases were also listed. The

TABLE 3

A group of 45 patients on whom data were insufficient, or time was too short, to permit anything more than a "medical impression"

Tuberculosis	
Active and uncomplicated.....	9
Active with pleural effusion.....	2
Active with abscess and lues.....	1
Active with abscess, lues and silicosis.....	1
Active with lues.....	1
Fibroid, quiescent, healing or healed.....	6
Total tuberculous.....	20
Chronic pneumonia, pneumonitis, atypical pneumonia, etc.....	
Cancer.....	6
Bronchiectasis.....	5
Nontuberculous effusion.....	3
Bronchial asthma, abscess, abscess and old lues, abscess and old tuberculosis, cystic lung, sickle cell anemia with general lymphadenopathy, sinusitis, catarrhal jaundice—1 each.....	3
	8
Total nontuberculous.....	25
Grand total.....	45

589 cases tested with tuberculin were charted for the five different quantitative reactions to tuberculin. The number of acute, subacute and probably active cases shown in column 3 is 318 in the 1:10,000 dilution; 53 in the 1:1,000 dilution; 6 in the 1:100; 2 in the 1:10; and zero in the negative group. The "acute" cases in the stronger dilutions were chiefly patients with severe infections who were being overwhelmed or desensitized. The 4th column shows the percentage of the total 589 cases tested. The 5th column lists the percentage at each dilution of tuberculin. The decrease in the percentage of acute types in the stronger dilutions is noteworthy.

The 6th column (for "fibroid types") shows even greater contrast, not so much for the total numbers of cases at each dilution as for the *percentage* at each dilu-

The complicating disease found in column 8 did not seem to have any noticeable effect on the tuberculin reaction in the cases studied. In the first three dilutions the percentages (column 9) are approximately the same for each dilution, but the last two include too few cases to permit any statistical evaluation. The group of 31 "complicated" cases showing a positive reaction to the 1:10,000

TABLE 4						
Relation of tuberculin sensitivity to acuity, chronicity and to nontuberculous diseases						
		ACUTE AND SUBACUTE		CHRONIC	TUBERCULOSIS COMPLICATED WITH OTHER DISEASES	NON-TUBERCULOUS DISEASES
1	2	3	4			

1		2		ACUTE AND SUBACUTE			CHRONIC		TUBERCULOSIS COMPLICATED WITH OTHER DISEASES		NONTUBERCULOSIS DISEASES				MISCELLANEOUS		
Dilution of tuberculin	Total cases with diagnosis of tuberculosis	Number	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
			Per cent of all cases tested	Per cent of tuberculous cases at each dilution	Number	Per cent of tuberculous cases at each dilution	Number	Per cent at each dilution									
1:10,000	363	318	54.0	87.6	14	3.9											
1:1,000	78	53	9.0	68.0	19	24.4											
1:100	18	6	1.0	33.3	11	61.1	31	8.5	Bronchiectasis								
1:10	3	2*	0	0	0	0	6	7.7	Sarcoidosis								
Negative	2†	0	0	0	0	0	1	5.6	Cancer								
Total....	464	379			44		2	0	Pneumonitis and atypical pneumonia								
							41	0	Other diseases†								
									Uncertain diagnosis								
									Total								

3	2	2	0	0	3	2
4	7	4	0	0	4	7
16	11	16			16	11

* One case was a terminal tuberculosis, the other an acute early case.

† One case was an old "fibroid" with diabetes, the other a

er.

‡ Includes abscess, diabetes

ama, cystic

4	7	2	1	2	5
16	11	20	4	32	42

One case was a terminal tuberculosis, the other an acute early case.

† One case was an old "fibroid" with diabetes, the other complicated with undulant fever.

‡ Includes abscess, diabetes, empyema, "cardiacs," nephritis, mycoses, rheumatics, asthma, cystic lung, Hodgkin's, lues, "atypical acid-fast infection," bacillus infection, lupoid, dermoid cysts. Sometimes two of these diseases were found together.

Dilution consisted of 12 cases of lues (some with syphilis), 3 cases of silicotuberculosis, 1 case of pyrotoxicosis.

dilution consisted of 12 cases of lues (some with added abscess), 3 cases of mitral disease, 3 cases of silicotuberculosis, 2 cases each of diabetes, bronchiectasis, thyrotoxicosis, rheumatism and pyocyaneus infection, and one each of hypertensive heart disease, bronchial asthma and massive pulmonary collapse. The next four columns (10, 11, 12 and 13) list the four most common nontuberculous diseases, namely bronchiectasis, sarcoidosis, cancer and pneumonitis. The percentages for the weaker dilutions, with the highest percentages in the cases positive to the 1:100 and 1:10 dilutions. The percentage figures (calculated on basis of totals in last column) for cancer in dilutions 1:10,000 down to

a negative in 1:10 dilution are 1.7 per cent, 2.8 per cent, 18.4 per cent, 10.5 per cent and 3.7 per cent, respectively. Bronchiectasis has percentages of no statistical significance for any group, while pneumonitis and sarcoidosis are almost exclusively negative to tuberculin. The reactions in all of these conditions would vary generally with the infection rate of tuberculosis in the community in which the patients have lived and with the age incidence of the nontuberculous disease in question and various other factors.

All other nontuberculous diseases are grouped in the third column from the end and are listed in the note to the table.

It is interesting to consider the nature of the few cases of tuberculosis negative to tuberculin, or only positive to high concentrations. In the 2 cases insensitive to the 1:10 dilution, the one (J. J., No. 40) classed as "active" had concomitant undulant fever. The tuberculosis improved and, as the undulant fever disappeared, the tuberculin reaction became positive in the 1:1,000 dilution. The other patient (M. K., No. 204) had an old fibroid tuberculosis; he had worked as a moulder for five years. An associated diabetes was also found after he entered the institution. A repeated tuberculin test after three months was found positive in 1:100 dilution. He died within four months. Autopsy completely confirmed the clinical findings. The diabetes probably resulted from a tremendous cyst which filled the middle third of the pancreas. However, all cases having diabetes do not have a negative or slightly positive reaction. There may have been a revival of latent allergy in these 2 cases, but the condition in the first case seemed to be due, partially at least, to the presence of another disease.

Since about a third of the tuberculous cases studied had some form of collapse therapy, it was important to observe the influence of collapse on the tuberculin reaction. According to Lichtenstein (43) patients undergoing collapse therapy manifested stronger reactions than cases not under collapse. In this series of 464 tuberculous patients there were 310 not receiving collapse therapy and 154 with some form of collapse. Of the former group, 238 (69.7 per cent) reacted to the 1:10,000 dilution and 72 (30.3 per cent) were positive to all other dilutions. In the group receiving collapse there were 125 (76.8 per cent) positive to the 1:1,000 dilution, while only 29 (23.2 per cent) were positive to all other dilutions. Although the difference is not great, it may lend some support to Lichtenstein's contention. No effort was made to classify the cases according to the results or duration of the collapse. There is enough difference between the cases receiving collapse and those not receiving collapse, however, to increase slightly the total number of cases found in the 1:10,000 dilution, but it would not make much difference in the use of the method in diagnosis.

It should be pointed out that the reason bacilli were not found in many cases was probably effective pneumothorax.

DISCUSSION

The net results of this study may at first appear to be equivocal or too limited for practical use, but like many other diagnostic methods it is useful only under specified conditions; the interpretation must be made with all other findings in

view. The quantitative tuberculin reaction has been shown to have strict limitations. It is of little positive value if used alone on the whole population or on any unselected group of patients. According to the work of Chadwick and Pope (24) only about 50 per cent of the population react to tuberculin. Probably only about 5 per cent of the reactions will be strong enough to indicate the possibility of activity, while according to surveys only 1 per cent of the population has clinically significant disease. The remainder of the reactions (45 per cent) approach complete insensitivity as the infections heal. Without collateral studies, such as roentgenograms, laboratory tests, etc., there is no way of distinguishing the significant from the nonsignificant disease. Strong tuberculin reactions alone, therefore, would probably be present in only about 20 per cent or less of cases, a number too low to be of any worth while diagnostic value. If, on the other hand, there are clinical or X-ray findings in the chest in addition, the percentages given in the tables afford a guide on which a strongly presumptive diagnosis may be made. Over 90 per cent (91.0 per cent of this study) of the reactors in the 1:10,000 group with positive clinical and X-ray findings and with sputum negative on three concentrations were found to have significant tuberculous. If, in addition, the definite nontuberculous cases are eliminated, the percentage possibilities of the group rise to around 96.0 per cent. Furthermore, if the probabilities of the cases with an uncertain diagnosis are considered, another 2.8 per cent is added. The remaining 1.2 per cent form an unknown group of patients at the 1:10,000 dilution in whom a more protracted search is necessary for a diagnosis. In the latter group may be included the 0.5 per cent definite errors found after a two-year interval.

Diagnosis was made in the cases positive in the stronger concentrations (1:1,000 dilution or stronger) by eliminating simultaneously the 43 cases (22.7 per cent of the group) of definite nontuberculous cases, and the 77 cases (40.5 per cent) whose sputum produced growth of tubercle bacilli on cultures. The remaining 70 cases (36.8 per cent) of the group required special studies for diagnosis. In the latter group there were 24 cases (12.6 per cent) with presumptive diagnosis of tuberculosis and 17 cases (8.9 per cent) with a presumptive diagnosis of nontuberculous disease. The remaining 29 cases (15.3 per cent) of the group, or 4.9 per cent of all negative cases, include the cases in the stronger dilutions which could only be classified as "medical impression."

The tuberculin reaction, however, contributes much in the diagnosis of these cases in a negative way. Positive results in the stronger dilutions rule out the possibilities of both the strong and the negative or near negative tuberculin reactions, thus compelling an entirely new line of search in diagnosis. It is worth more to know that the patient has a weak reaction than not to know anything about the skin reaction at all.

The greatest value of quantitative tuberculin tests is in the negative reactions. If, for the sake of argument, we do not consider sarcoidosis³ as a form of tuber-

³ The question of the nature of sarcoidosis is still too controversial to permit its definite classification as tuberculosis. The failure to react to tuberculin at least places it apart. It is true that sarcoidosis hovers around tuberculosis sometimes like "smoke to fire," but

culosis, only in the rarest circumstances will a case of significant tuberculosis be found in an insensitive person, unless that person is moribund or has a superimposed complicating disease. Even negative reactors to a 1:100 dilution or stronger, except for the instances just mentioned, must be viewed as nontuberculous until proved otherwise. Negative tuberculin reactions, once rare in everybody but children, now are found in practically all ages and under varying circumstances.

The largest and most important group of negative reactors includes the people who have never been infected with the tubercle bacillus. Another group of negative reactors are the people who have recovered from the first infection and have apparently lost all sensitivity. Long (49) reported that 11 per cent lost their sensitivity in 2,490 cases during a ten-year period. Opie (50) reported about 5 per cent and Sayé (51) 1.6 per cent of *visible lesions* in tuberculin-negative cases. No doubt there are many more if invisible lesions are included, but there is no way at present of proving this statement. The healing of a small tuberculous focus with a corresponding disappearance of the tuberculin reaction is what may be expected in cases with small foci of several years' duration. Westwater (41) observed that the tuberculin reaction was strongest in recent lesions and diminished with time whether the lesions were primary in children, or recently ulcerative types in adults. With healing and fibrosis the tuberculin reaction gradually faded. Opie and McPhedran (31) and Cummins (52) came to somewhat similar conclusions, but Lichtenstein believes that the overwhelming of a patient with tuberculo-protein brings about a reduced sensitivity and that encapsulation or prevention of absorption tends to increase the reaction. It is possible for a reaction to be augmented by lifting the dampening effect of tuberculo-protein when the infection is acute, but it is probable that patients with healing lesions gradually lose their sensitivity due to a disappearance of the antigen so that they become entirely insensitive to ordinary methods of testing.

Evidence is accumulating, however, that the infected host, after becoming negative, never does return to a state identical to that before infection.

The work of Willis (53) has shown that guinea pigs in which an R1 infection healed did not react to tuberculin. But within four days following a reinfection with H37 their reactions returned. Sayé (11) accomplished the same result with BCG in man. A previous injection of tuberculin usually became "reawakened" within about nine days. In addition, there is described an altered reaction at the

few cases of proved sarcoidosis have revealed any tubercle bacilli, when all possibilities of contamination by tubercle bacilli have been ruled out. Not one of the 12 cases in the series revealed any tubercle bacilli, and the demonstration of Pickert and Löwenstein's (46) "procutins" and "anticutins" was not accomplished in spite of much effort. If it is ultimately proved to be true that sarcoidosis is a "tuberculoïd" condition and that a special allergic state exists, the "specific energy" of Jadassohn (33) or "positive energy" of Hayek (47) or some similar explanation may be used. It is an attractive theory to consider sarcoidosis as a noncaseating tuberculosis as Pinner (48) has done, but until the theory has been established, it seems logical to regard it, in studies of this nature at least, as a nontuberculous disease.

site of the antigen injection to the effect that a hardened nodule appears after twenty-four hours' time. The nodule may ulcerate like the reaction produced in any sensitized animal and is strong proof of a former infection. Novak and Kruglick (54) have restored extinct ("anamnestic") reactions simply by performing repeated tuberculin reactions.

Similar to these phenomena may be listed the "infratuberculin" reaction of Arlindo de Assis (55), Rosemberg (56) and others who describe the awakening of tuberculin reaction at the site of injection of tuberculin by administering a second dose of BCG in the "preallergic" period as well as the "postallergic" phase of the reaction.

The effect of overwhelming tuberculosis has been included in conditions producing negative reactions, but it is probable that few, if any cases, ever become completely insensitive, as the work of Happ and Casparis (57) and Willis and Jocz (58) tends to show.

Another phenomenon known for a long time is that certain superimposed diseases either diminish or dissipate the reaction as long as the associated disease lasts. Influenza (59), measles (60), pregnancy (61) have been mentioned as disturbing factors. The case of undulant fever in this series illustrates this phenomenon. In most of the overwhelming infections or superimposed conditions the clinical findings are usually of such a nature that no other proof is necessary for a diagnosis. There may be other yet undetermined factors and combinations of conditions not yet known which may influence the strength of the reaction.

For a more complete understanding of the possibilities of the tuberculin reaction, and for outlining future plans for studying the phenomenon, it is now appropriate to discuss briefly the evolution of the reaction in the body and the possible changes taking place in the waxing and waning of the disease.

In the uninfected host, in whom no hypersensitiveness has ever been developed, the skin probably does not react specifically to any dosage of tuberculin, although nonspecific intoxication of tissues may result from huge doses. Furthermore, tuberculin as used in testing, apparently does not produce skin sensitivity (62, 63). The state of the skin in an uninfected person has been called normal "anergy" or "normergy" by Ranke (64) or "absolute anergy" by Hayek (47).

The first phase is the period existing between the time of infection and the development of hypersensitiveness. This is properly termed the preallergic period. There is no doubt that a certain intoxication or stimulation of the cells is going on during this period. The tuberculin reaction is still negative, but apparently "infratuberculin" reaction may be elicited. It requires from three weeks to three months for a typical reaction to develop in the cells, so that a measurable hypersensitiveness may be recognized. After the preallergic period, the true allergic period appears, the length of which varies considerably, depending on the size of dosage and rapidity of healing and many other factors. In the early stages of the disease the reaction becomes strongly positive and remains strongly positive during the early encapsulation of the focus. As time passes, the strength of the reaction probably diminishes gradually until the bacilli are all dead and

all antigenic substances are eliminated or destroyed. The reaction may fluctuate from time to time, depending upon various factors which cause a liberation of antigen or an encapsulation of antigen. In acute advanced disease the liberation of excess antigen tends to decrease the magnitude of the reaction while in healing disease the decrease in free antigen tends to allow the sensitized skin to react. In healed disease the skin sensitivity tends to disappear.

The time between the death of the bacilli and the total disappearance of the tuberculin reaction is still speculative, but it probably extends from two to many years after the death of the bacilli, depending on the size and activity of the lesions, the virulence of the bacilli and the conditions of the host. In support of such a possibility there are the observations of Blair and Galland (38) who found in children with primary infections no cases negative to the 1:10,000 dilution under 8 years of age, showing that the infections were still in active evolution; whereas the number of negative cases increased after that time. Westwater (41) also reported that the tuberculin reactions increase in severity up to 4 to 5 years of age, then decrease to 10 years of age. Johnston, Howard and Maroney (65) and others made similar observations. In the same connection, it is pertinent to recall that Poulsen and Andersen (66) and Sayé (51) were able to find living bacilli in stomach lavage of children with healing disease for only about three years.

Strong supportive evidence of the limits of time on the evolution of the tuberculin reaction is afforded also by the experimental observations of Willis (53) who found that sensitivity to weak dilutions of tuberculin disappears within two years. Sayé (11), Ferguson (67) and Rosenthal (68) observed the fading or disappearance of the tuberculin reaction following vaccination with BCG within two to five years in a large percentage of cases.

Aronson, Parr and Saylor (69) showed that only 39.2 per cent of one group reacted to the first dilution of PPD one year after inoculation. In general, however, the majority retained sensitivity to stronger dilutions up to five years. The authors noted variation in results depending on the media used for growing the vaccine, age of growth, dosage and persons tested. In most of these observations there has been no way of determining the number of natural infections which would tend to prolong the sensitivity indefinitely. In fact, it is reasonably certain that some of the vaccinated persons received such natural infections. Bogen and Loomis (70) followed the course of tuberculin sensitivity in an infant vaccinated with dead BCG and noted that a "slight positive" reaction was present for three to four years, but Bogen (71) states that a reaction could be elicited after twelve years by using large doses of tuberculin. The length of persistence of reaction in vaccinated cases might well be considered the minimum for all tuberculous infections because it is one of the most benign of tuberculous infections. Since Aronson, Parr and Saylor (69) and Rosenthal (72) showed that bacilli soon disappear from the lesions, it may be reasonably assumed that the BCG dies out soon after inoculation. Practically the whole period, therefore, represents the fading period of the reaction from a small and avirulent infection.

The total length of time a reaction may persist in a true tuberculous infection

depends on the time of survival of the bacilli as well as the size of the lesions and perhaps other factors. As to the persistence of bacilli in the lesions; the time varies from a few years to a life-time. As the healing period differs for each individual, it is difficult to say when the bacilli are all dead. The time has been approximated by Sweany, Levinson and Stadnichenko (73) in small tubercles taken from people dying of causes other than tuberculosis. By estimating the age based on morphological changes, these authors reported that the number of bacilli decreased in the tubercles for a period of from one to ten years, with the average revealing no bacilli after about two and a half years, the majority after five years, and practically none after seven years. When the average period of survival of the bacilli in small tubercles is added to the minimum period of persistence of the tuberculin reaction based on the reaction produced by BCG the total minimum period of persistence of the ordinary tuberculin reaction in small healing tuberculous infections would be from five to ten years. Large tubercles require longer to heal and no doubt the reaction would persist proportionally longer.

In one case, which I was able to follow, there was a complete disappearance of the tuberculin reaction to 10 mg. of OT at the age of 31 after what appeared to be a primary infection around the age of 5. During early school years this female patient had severe "winter bronchitis" for several years. At the age of 12 an X-ray film revealed a large calcified complex in the left lung and hilum. The tuberculin reaction at that time was strongly positive to OT, 1:1,000. Several X-ray examinations up to the age of 18 showed a gradual shrinking of the hilar lesion, but the tuberculin reaction was still moderately positive to the 1:1,000 dilution of OT. On several X-ray examinations during the next thirteen years there was no significant change in the appearance of the lesions, but the tuberculin reaction became negative to 10 mg. OT. The minimum time of disappearance of this rather large lesion was probably around fifteen years and the maximum around twenty-five years.

With the various possibilities in mind, it is obvious that there are far greater opportunities for use of the tuberculin reaction than is commonly appreciated. While it may fall far short of a diagnostic agent to detect "clinically active" tuberculosis, the reaction rates high in the scale of useful methods in the diagnosis of chest diseases. It deserves to be the first procedure after history, physical, X-ray and sputum examination. In fact, it should be simultaneous with the other studies in all patients with negative sputum. It may be stated without reservation that tuberculosis is the principal disease to detect or eliminate in chest work and the quantitative tuberculin reaction is one of the most valuable aids in the achievement of this result.

The principal drawback at present is a lack of understanding of all phases of the reaction and a lack of uniform procedure. The first step towards uniformity should be the adoption of a standardized tuberculin. While OT may be used as in this study, there should be no hesitancy in using also PPD. In fact, it would seem to be the tuberculin of choice. PPD can be used to greater advantage in quantitative tuberculin tests by adding a ten times larger dosage as the one

recommended for the No. 2 dilution. Jensen and associates (75) have recommended the latter dilution. The two standard dilutions separate roughly the "probably active" cases (positive on first injection of 0.000,02 mg.) from the "probably inactive" group and desensitized cases (negative to the No. 2 dilution—0.005 mg.). The third dilution would identify most of the completely insensitive cases. A fourth higher dilution may also be used to correspond to about a 1:50,000 dilution (0.002 mg.) of OT which is favored by some for ruling out certain types of active tuberculosis; this quantity of PPD would be about 0.000,004 mg.

For ordinary purposes, however, the higher dilutions are either unnecessary or the results may be estimated by measuring the size of the reaction following the injection of 0.01 mg. OT or 0.000,02 mg. PPD after the method of Westwater's single injection technique. The objection to Westwater's method is that single injections of 0.1 mg. OT sometimes cause severe reactions.

Finally, long continued serial studies of different groups and races at different ages and with different types of treatment with and without complications, would remove many uncertainties and help to establish the test on a firmer basis. Herein lies the possibility of perfecting the method to help establish a diagnosis, especially in sputum-negative cases; to assist as far as possible in the appraisal of activity and healing in tuberculosis and of separating nontuberculous conditions.

SUMMARY

A detailed study of the value of tuberculin in diagnosis has been reported on 600 sputum-negative cases representing 32.0 per cent of all admissions to the Municipal Tuberculosis Sanitarium of Chicago over a period of 498 days. The cases consisted of 464 tuberculous and 91 nontuberculous with 45 of uncertain diagnosis. Of this number, 589 were tested by a quantitative tuberculin reaction. Old Tuberculin (Parke, Davis and Company) was given by the Mantoux method in four dilutions: 1:10,000 (0.01 mg.), 1:1,000 (0.1 mg.), 1:100 (1.0 mg.) and 1:10 (10 mg.).

When used alone, the quantitative tuberculin reaction has significant limitations.

When used in conjunction with other means of diagnosis, as in the series reported, especially with chest X-ray films, quantitative tuberculin is one of the most valuable diagnostic aids available. In the presence of demonstrable disease in the chest, 91.0 per cent of the cases positive to the 1:10,000 dilution were found to be tuberculous with a known error of only 0.5 per cent to date. Of the 9.0 per cent remaining, 5.76 per cent were rather promptly found to be nontuberculous with no known errors to date. The other 3.24 per cent included the cases on which only "medical impressions" could be given. Since many of these incomplete diagnoses were found later to be partially or wholly correct, the number of diagnostic failures in the cases positive to the 1:10,000 dilution were probably not over 2 per cent.

The 1:1,000 and 1:100 dilutions of tuberculin offer no positive aid in diagnosis.

There is some "negative" value in that the particular case is *not strongly positive* or *completely negative*, but has already been infected.

In the cases positive to the 1:10 dilution (usually small in number) only one of the 3 cases of tuberculosis in the series was free from serious complications.

In the 2 cases negative to the 1:10 dilution, both were complicated by other serious diseases.

The absence of tuberculous disease is almost certain (97.1 percent) in uncomplicated cases negative to the 1:100 dilution.

At present, the tuberculin reaction is not dependable in detecting activity, significant lesions, or prognosis.

The tuberculin reaction would seem to deserve a more general understanding and usage, not only because of the progressive decrease in infection incidence, but because of the diagnostic possibilities, when used quantitatively, of finding tuberculosis in the strongly positive reactors and more especially in ruling out tuberculosis in the weak reactors.

A plea is made for a standardization of the reaction, based preferably on PPD with stronger and weaker dilutions added to those already recommended.

SUMARIO

La Tuberculina en el Diagnóstico

Este estudio pormenorizado del valor de la tuberculina en el diagnóstico comprende 600 casos de esputo negativo que representan 32 por ciento de todos los ingresos en el Sanatorio Municipal para Tuberculosos de Chicago durante un período de 498 días. Los casos comprendían 464 tuberculosos y 91 no tuberculosos más 45 de diagnóstico incierto. De ese total, se comprobó a 589 con una reacción cuantitativa a la tuberculina. La Tuberculina Antigua (Parke, Davis & Cía.) fué administrada con la técnica de Mantoux a cuatro diluciones: 1:10,000 (0.01 mgm.), 1:1,000 (0.1 mgm.), 1:100 (1.0 mgm.) y 1:10 (10 mgm.).

Empleada por sí sola, la reacción cuantitativa a la tuberculina muestra limitaciones significativas.

Empleada, en cambio, en unión de otros medios de diagnóstico, como en la serie descrita, sobre todo con películas radiográficas del tórax, la tuberculino-reacción cuantitativa constituye uno de los auxiliares más valiosos para el diagnóstico. En presencia de enfermedad reconocible del tórax, 91 por ciento de los casos positivos a la dilución al 1:10,000 resultaron tuberculosos con un error conocido de no más de 0.5 por ciento hasta la fecha. Del 9 por ciento restante, en 5.76 por ciento se descubrió con bastante prontitud que no eran tuberculosos, sin errores conocidos hasta ahora. El otro 3.24 por ciento comprendía los casos en que no se contaba más que con "impresiones médicas". Como muchos de estos diagnósticos incompletos resultaron después parcial o totalmente exactos, la proporción de fracasos diagnósticos en los casos positivos a la dilución al 1:10,000 no pasó probablemente de 2 por ciento.

Las diluciones de tuberculina al 1:1,000 y 1:100 no ofrecen ayuda positiva en el diagnóstico, aunque encierra cierto valor "negativo" el hecho de que el

caso que *no es fuertemente positivo ni completamente negativo*, ya está infectado.

En los casos positivos a la dilución al 1:10 (por lo general pocos), sólo uno de los 3 casos de tuberculosis del grupo no mostraba complicaciones graves.

De los 2 casos negativos a la dilución al 1:10, ambos estaban complicados con otras dolencias graves.

La ausencia de tuberculosis es casi segura (97.1 por ciento) en los casos sin complicaciones negativos a la dilución al 1:100.

Hoy por hoy, la reacción a la tuberculina no resulta fehaciente para descubrir actividad, lesiones importantes o pronóstico.

La reacción a la tuberculina parece ser digna de comprensión y empleo más generales, no tan sólo debido a la disminución gradual de la incidencia de infección, sino también, cuando se utiliza cuantitativamente, a la posibilidad de descubrir tuberculosis en los reactores fuertemente positivos y más en particular de excluir el mal en los reactores débiles.

Abógase por la estandarización de la prueba, a base de preferencia de PPD y agregando diluciones más altas y más bajas a las ya recomendadas.

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DECLINE IN TUBERCULOSIS

The Death Rate Falls to Tell the Entire Story

MARY DEMPSEY¹

The *best available single index* as to the status of tuberculosis control is and always has been the mortality rate from this disease. Similarly, the best measure of the success of the tuberculosis program is evidenced by the steady decline in the death rate during the past several decades. One is impressed by the fact, for example, that tuberculosis mortality in the country as a whole has declined 53 per cent between 1924 and 1944.

This drop in tuberculosis mortality varies widely in the sex and color groups. The greatest decline in the past twenty years, for example, has been registered in the death rate for white women among whom the drop was 67 per cent; among non-white men, on the other hand, tuberculosis mortality declined but 42 per cent during the same period. (According to the Federal Census of 1940, 99.4 per cent of all non-whites in the United States were Negroes; hence the two groups are almost identical.)

Table 1 shows, for each sex and color group, the tuberculosis death rates in the past two decades, as well as the percentage decline in mortality.

TABLE 1
Tuberculosis death rates in 1924, 1934, and 1944 and percentage decline in the death rate, classified by sex and color: United States

SEX AND COLOR	TUBERCULOSIS DEATH RATE			PERCENTAGE DECLINE IN TUBERCULOSIS DEATH RATE	
	1944	1934	1924	1924-1944	1934-1944
All groups.....	41.3	56.7	87.9	53.0	27.2
White.....	33.7	46.2	74.9	55.0	27.1
Male.....	45.0	52.7	79.3	43.3	14.6
Female.....	23.3	39.6	70.4	66.9	41.2
Non-white.....	106.2	148.8	218.6	51.4	28.6
Male.....	122.7	156.9	215.0	42.1	21.8
Female.....	91.3	140.8	222.3	58.9	35.2

For none of the major causes of death has a mortality decline been recorded which in any sense compares favorably with the drop in the tuberculosis death rate. Quite the contrary; in fact, mortality from heart diseases, cancer, and certain other leading causes has increased rather steadily while that from tuberculosis has been dropping continuously.

¹ Statistician, National Tuberculosis Association, 1790 Broadway, New York 19, New York.

In 1944 the death rate from heart diseases in the United States as a whole was 315.4 per 100,000 population; while the rate caused by cancer was 129.1. Tuberculosis, the seventh cause of death, trailed along with a mortality rate of 41.3 per 100,000. Table 2 gives the 1944 death rates from these three major causes for each sex and color group.

TABLE 2

Death rates per 100,000 population from each specified cause, classified by sex and color: United States, 1944

SEX AND COLOR	DEATH RATE PER 100,000 POPULATION IN 1944		
	Heart diseases	Cancer	Tuberculosis
All groups	315.4	129.1	41.3
White.....	310.1	128.8	33.7
Male.....	398.6	135.5	45.0
Female.....	254.2	133.3	23.3
Non-white.....	239.0	81.9	106.2
Male.....	274.3	75.6	122.7
Female.....	220.6	92.2	91.3

These death rates, though admittedly correct, fail to tell the whole story. They tend to be somewhat misleading as to the relative importance of these three diseases since so many more of those who die of heart diseases and of cancer are elderly than is the case with those who die of tuberculosis. Moreover, tuberculosis is not only communicable but is likewise preventable to a vastly greater extent than either heart diseases or cancer.

POTENTIAL YEARS OF LIFE LOST BY THOSE WHO DIE OF THREE MAJOR CAUSES

In order to demonstrate more vividly the seriousness of a disease which may lead to prolonged illness and death in youth or middle age, a computation has been made showing the potential loss in years of life resulting from deaths from heart diseases, cancer, and tuberculosis in 1944. This computation is based on the expectation of life at birth, as published by the Metropolitan Life Insurance Company in its Statistical Bulletin for May, 1946.

Separate analyses have been made for white and non-white men and women, since these groups vary widely not only as to their expectation of life, but in addition the age distribution of deaths from certain causes follows a very different pattern in each sex and color group. In fact, if death rates for all diseases are considered, the mortality from tuberculosis shows the most marked variations for race and sex.

The method used in this computation is simple indeed. For example, the average white woman may expect to live sixty-nine years. If she dies at the age of 24 from tuberculosis, she has lost forty-five potential years of life, whereas if she dies at 62 of heart disease, she has lost but seven potential years.

In the aggregate, 1,929,953 potential years of life were lost by all Americans who died of heart diseases in 1944, compared with 1,287,245 potential years lost by those who died of cancer and 1,175,500 by those who died of tuberculosis in that year. In other words, because of the differences in the ages of those who died from these diseases, the potential loss in years of life occasioned by deaths from tuberculosis is within 10 per cent of the loss caused by cancer, even though the tuberculosis death rate is but 32 per cent of the cancer death rate.

In spite of the fact that the mortality from heart diseases is seven and one-half times as high as that from tuberculosis, the potential years of life lost by those who died of heart diseases in 1944 were less than twice as numerous as the years lost by those who died of tuberculosis in the same year. (See table 3.)

TABLE 3

*Potential years of life lost by those who died of specified cause, classified by sex and color:
United States, 1944*

SEX AND COLOR	POTENTIAL YEARS OF LIFE LOST BY THOSE WHO DIED OF SPECIFIED CAUSE IN 1944		
	Heart diseases	Cancer	Tuberculosis
All groups.....	1,929,953	1,287,245	1,175,500
White.....	1,739,902	1,204,250	830,306
Male.....	979,107	393,948	422,513
Female.....	760,795	810,302	407,793
Non-white.....	190,051	82,995	345,194
Male.....	76,676	21,878	153,664
Female.....	113,375	61,117	191,530

Table 3 indicates that in 1944 tuberculosis caused greater potential loss in years of life than did cancer so far as white men are concerned, though among white women the potential loss from tuberculosis is only half that from cancer. Among non-white men the potential loss occasioned by deaths from tuberculosis was twice that caused by heart diseases and seven times the loss resulting from cancer deaths.

Tuberculosis is by far the most serious of the three diseases so far as the potential loss of life to non-white women is concerned. Table 3 serves to point up the widely recognized fact that tuberculosis constitutes the most serious public health problem among non-white races.

The fact that nowadays nearly 1,200,000 potential years of life are lost by those who die of tuberculosis in *one year alone* should be stressed. If the number of tuberculosis deaths should remain stationary and if the deaths were to continue to occur in the same sex, age, and color groups, then 12,000,000 potential years of life would be cut off for those who die of tuberculosis in a decade and

30,000,000 years would be lost by those who die in a generation (twenty-five years).

Even this estimate errs on the side of understatement for at least two reasons: (1) To be more nearly accurate the potential years of life lost by persons who die of tuberculosis should be computed on the basis of life expectancy at the actual age at death which is always higher than life expectancy at birth; for reasons of expediency this more exact method of computation did not prove feasible. (2) Cognizance should be taken of the many, many years of activity lost by patients who must spend long months and years in bed prior to recovery or death as the case may be.

While 1,175,500 potential years of life were lost by those who died of tuberculosis in 1944, the comparable loss resulting from tuberculosis deaths in 1943 was 1,238,645 years, a decline in one year of 5.1 per cent. (See table 4.) The mortality from tuberculosis dropped from 42.6 per 100,000 population in 1943 to 41.3 in 1944, or 3.1 per cent.

The decline in potential years of life lost by those who died of tuberculosis in 1944, as compared with 1943, exceeds the decline in the death rate because each year the proportion of tuberculosis deaths which occur among younger age groups becomes less and less. This change in the age distribution of tuberculosis deaths which has been apparent for the last two decades is in itself an achievement so far as tuberculosis control is concerned, though a lesser one than the decline in the death rate. In other words, as so frequently stated, tuberculosis becomes increasingly a disease of adults and particularly of adult men.

TABLE 4
Potential years of life lost by those who died of tuberculosis in 1943 and 1944 and percentage of decline in this loss, classified by sex and color: United States

SEX AND COLOR	POTENTIAL YEARS OF LIFE LOST BY THOSE WHO DIED OF TUBERCULOSIS IN SPECIFIED YEAR		
	1944	1943	Percentage of decline
All groups.....	1,175,500	1,238,645	5.1
White.....	830,306	868,479	4.4
Male.....	422,513	442,810	4.6
Female.....	407,793	425,669	4.2
Non-white.....	345,194	370,166	6.7
Male.....	153,664	165,936	7.4
Female.....	191,530	204,230	6.2

MEDIAN AGE AT DEATH

Analysis of the median ages at death for three major causes offers another way of pointing out the fact that tuberculosis causes a greater loss, comparatively speaking, than is indicated by the death rate. In table 5 median ages at death

from heart diseases, cancer and tuberculosis are shown for each sex and color group and compared with the expectation of life at birth for each group.

From this table it is evident that, with the exception of non-white females, the median ages of all groups of persons who died of heart diseases in 1944 were older than their expectation of life at birth. Moreover, the median ages at death of men (both white and non-white) who died of cancer in 1944 were older than their expectation of life at birth. On the other hand, the median ages of white and non-white women who died of cancer in 1944 were in each instance five and one-half years younger than their expectation of life at birth.

In the case of those who died of tuberculosis in 1944, however, the median age at death ranged from thirteen to thirty-one years younger than the expectation of life at birth for the various sex and color groups. The comparatively low median ages at death from tuberculosis illustrate the point so often made with reference to the social problems created by illness and death from tuberculosis among young and middle-aged persons.

TABLE 5

Median age at death from specified cause and expectation of life at birth, classified by sex and color: United States, 1944

SEX AND COLOR	MEDIAN AGE AT DEATH			EXPECTATION OF LIFE AT BIRTH
	Heart diseases	Cancer	Tuberculosis	
All groups.....	69.4	64.2	43.0	65.12
White.....	70.0	64.8	47.1	66.25
Male.....	67.9	66.0	50.4	63.55
Female.....	72.9	63.5	38.3	68.95
Non-white.....	59.9	56.0	32.9	57.14
Male.....	60.3	59.1	37.7	55.30
Female.....	54.4	53.5	28.4	58.99

In table 6 the median age at death has likewise been computed for those who died of tuberculosis in 1944, 1934, and 1924. Data for 1924 possess less significance than those for the other two years because in 1924 only 40 states were included in the death registration area, whereas since 1933 all states have been included. Inasmuch as 3 (Alabama, Arkansas and Texas) of the 13 southern states with 10 per cent or more Negro population were not included in the area in 1924, the non-white group is not fully represented in the mortality statistics for that year.

In 1944 those who died of tuberculosis were on the average nearly ten years older than those who died of the same cause in 1924. In spite of the more complete representation of non-whites in 1934 and 1944, it is of interest to note that the progress made in prolonging the lives of the tuberculous who died in the recent decade has kept pace with the progress in the earlier one.

The most noticeable advance in the median age at death is that of white men

who in 1944 were eleven and one-half years older on the average when they died of tuberculosis than were those who died of the disease in 1924. The difference in the age at death among white women was seven years and among non-white men it was seven and one-half years. Non-white women, on the other hand, were but two years older when they died of tuberculosis in 1944 than were those who died of this disease twenty years earlier.

When all sex and color groups are considered, the percentage advance in median age at death from tuberculosis between 1924 and 1944 was approximately half as great as the percentage decline in the tuberculosis death rate. But the relationship of these two types of changes varies greatly in the sex and color groups.

TABLE 6
Median age at death from tuberculosis in 1924, 1934, and 1944 and percentage advance in median age at death, classified by sex and color: United States

SEX AND COLOR	MEDIAN AGE AT DEATH FROM TUBERCULOSIS			PERCENTAGE ADVANCE IN MEDIAN AGE AT DEATH FROM TUBERCULOSIS	
	1944	1934	1924	1924-1944	1934-1944
All groups.....	43.0	37.9	33.3	29.1	13.5
White.....	47.1	41.7	35.0	34.6	12.9
Male.....	50.4	45.0	38.8	29.9	12.0
Female.....	37.7	35.8	30.8	22.4	5.3
Non-white.....	32.9	30.0	28.0	17.5	9.7
Male.....	37.7	33.4	30.2	24.8	12.9
Female.....	28.4	27.3	26.1	8.8	4.0

DISCUSSION

It would prove very fascinating, indeed, to offer some answers to these seemingly contradictory findings, if we were not keenly aware that the answers are altogether problematical, being based largely on conjecture.

Speaking of white people only, why is it that the tuberculosis death rate among women is so much lower than among men and is declining so much more rapidly, while at the same time the median age of women who die of tuberculosis is so much younger than that of the male decedents? To complicate this inquiry still further, what is the reason that the median age at death of white women decedents is being pushed up so much more slowly than is the median age at death among white men?

One might suggest that women are either less exposed or more resistant to tuberculous infection (or reinfection) than is the case with men. But once women actually acquire the disease they seem to lack the ability of men to hold it at bay and keep on living for a period of years. In other words, the tuber-

eulosis control program appears to have been quite successful among women so far as reduction of the death rate is concerned, while in the case of men the principal evidence of success has to do with the advancing age at death.

Studies of tuberculin testing among young men and women of the same age groups and of similar economic status show a higher percentage of reactors among young men. For example, tests made on freshmen in certain large eastern colleges a few years ago indicated that 21.3 per cent of the boys and 16.0 per cent of the girls were reactors.

Mass X-ray surveys usually show more cases of tuberculosis among men than among women, but some of these studies are fragmentary in nature while in most of them the persons X-rayed have been assembled with some bias in their selection.

Mass case-finding service was initiated on a large scale as a military and industrial activity. Since this is the case, the majority of persons X-rayed to date have been men. When women have been included in these studies they are often concentrated in younger age groups and sometimes in different economic groups. The women X-rayed in a large factory, for example, may be quite largely white-collar employees or young factory hands, while the men examined are likely to be skilled workmen or semiskilled workers. In other words, few data of a comprehensive nature are available to show the comparative prevalence of tuberculosis among men and women in the same age, color, and economic groups.

SUMMARY AND CONCLUSIONS

For many years past great emphasis has been placed on the steadily declining tuberculosis death rate as the most significant evaluation of tuberculosis control. Too little importance has been attached to a secondary result, namely, that those who die of tuberculosis are not only fewer in number each year, but the median age at death becomes somewhat higher. Some persons aware of these two encouraging developments have arrived at the erroneous conclusion that tuberculosis no longer represents a serious problem in this country.

Deaths from tuberculosis occur at much younger ages even to-day than do deaths from heart diseases and cancer.

The potential loss in years of life occasioned by deaths from tuberculosis in 1944 is within 10 per cent of the loss caused by cancer, even though the tuberculosis death rate is but 32 per cent of the cancer death rate. The tuberculosis mortality is less than one-seventh that from heart diseases although the potential years of life lost by those who died of tuberculosis in 1944 were more than half as numerous as the comparable loss traceable to heart diseases in the same year.

In 1944, the median ages at death from tuberculosis ranged from thirteen to thirty-one years younger than the expectation of life at birth for the various sex and color groups.

These findings indicate that tuberculosis still constitutes one of our most serious social problems. Since *all* cases of tuberculosis are preventable, the disease likewise still presents a more serious public health problem than do other

major causes of death. Tuberculosis must unquestionably be recognized as the most serious public health problem among non-white races; moreover, the seriousness of this disease among white men has never been given proper consideration.

SUMARIO Y CONCLUSIONES

La Disminución de la Tuberculosis y la Baja en la Mortalidad

Desde hace muchos años se ha hecho mucho hincapié en la baja constante de la mortalidad tuberculosa como valor más significativo en la lucha antituberculosa, sin conceder suficiente importancia a una consecuencia secundaria, o sea, que en los que mueren de tuberculosis la edad media a la muerte resulta algo mayor. Sin embargo, esos dos desenvolvimientos alentadores no justifican la conclusión errónea de que la tuberculosis ha dejado de constituir un problema grave en los Estados Unidos.

Las muertes de tuberculosis, aun hoy día, sobrevienen a una edad mucho menor que las debidas a las cardiopatías y el cáncer.

La pérdida potencial en años de vida ocasionada por las muertes de tuberculosis en 1944 apenas se separa en 10 por ciento de la ocasionada por el cáncer, aunque la mortalidad tuberculosa no constituye más de 32 por ciento de la cancerosa. La mortalidad tuberculosa no representa ni la séptima parte de la debida a las cardiopatías aunque los años de vida potencial perdidos por los que murieron de tuberculosis en 1944 fueron más de la mitad de la comparable pérdida imputable a las enfermedades del corazón en dicho año.

En 1944, las edades medias de los muertos de tuberculosis fueron de 13 a 31 años menores que la expectativa de vida al nacer para los varios grupos de sexo y color (raza).

Esos hallazgos indican que la tuberculosis sigue constituyendo uno de nuestros más graves problemas sociales. Visto que *todos* los casos de tuberculosis son prevenibles, la enfermedad igualmente plantea todavía un problema sanitario más serio que otras grandes causas de muerte. La tuberculosis debe ser indiscutiblemente reconocida como el problema sanitario más grave entre las razas distintas de la blanca; y además su gravedad en el blanco jamás ha recibido la consideración que merece.

EDITORIAL

Rehabilitation and Prognosis

In the last few issues of the REVIEW, several papers, book reviews and abstracts on rehabilitation work appeared. This provides the opportunity for some remarks which have frequently been heard in informal gatherings but have rarely, if ever, appeared in print. The rapid development and expansion of rehabilitation work have created the need for specially trained persons, practically for a new profession, whose educational qualifications are still vaguely defined and are still *sub judice*, a profession which still is in need of clearer demarcation against the fields of occupational therapy and social service, out of which an ever decreasing percentage of available rehabilitation workers have grown. The actual status of this new profession has some similarity to that of the two fields of endeavor just mentioned, about twenty-five years ago, when good will and humane interest were taken for granted in occupational therapists and social workers, when professional objectivity was hoped for but ill defined and rarely in evidence.

It is generally accepted policy that the first tentative steps toward rehabilitation should be taken as soon as the patient's clinical status permits and that the period of hospitalization should be used to the fullest extent for purposeful activities directed toward the final aim of physical, psychic and economic rehabilitation. But the influence of old-fashioned occupational therapy is still so strong in some institutions that the patient is still taught, far too much, how to kill time with inherently useless hobbies and handicrafts, instead of how to use his time for his final rehabilitation. Not only from the point of view of rehabilitation, but also from a strictly medical point of view, such residues of past decades are to be deplored, because any constructive, purposeful activity is far better psychotherapy than a playful waste of leisure time.

But these diseases of early childhood are probably less important than two other problems. That rehabilitation work is a necessary and important part of the successful treatment of many patients is quite generally accepted; it has come into its own during the last quarter of a century, in word and program, if not in action and reported results. If advocates of any medical or surgical treatment of tuberculosis had, for twenty or even for ten years, written profusely on plans, methods, set-ups, theory and—the philosophy (a beloved misnomer!)—of some treatment, without publishing statistically acceptable reports of results in terms of numerically significant case reports, they would, by now, find their treatment pretty well discredited. But this is, in essence, the present status of rehabilitation work. The few exceptions of reports on final results are so well known that they need not be quoted. But since most of them refer to special and limited phases of rehabilitation—limited either to the one facet of physical rehabilitation or to one or two occupational aims, or to one particular type of patients—rehabilitation work is still in the unsatisfactory phase when its necessity is beyond question but its actual results are quite insufficiently known. These lines are

written in the hope and expectation that they may encourage the publication of the numerical results of modern rehabilitation work in all its aspects. Data on which such publications should be based must surely be in the files of many agencies. We must know what broad rehabilitation work can do, lest financial support be diminished or withdrawn.

The second problem also would seem to be soluble. When rehabilitation workers select patients or so-called ex-patients for rehabilitation (which frequently means considerable financial investment) they must do so, explicitly or implicitly, on the basis of prognosis. But we have neither prognostic criteria nor a prognostic classification, generally accepted. Minimal qualifications for patients to be rehabilitated are usually established by regulations or even by law. In these circumstances, the diagnostic terms "quiescent," "apparently arrested" and "arrested" form the basis for some understanding between medical men and non-medical rehabilitation workers. These terms do not contain any element of prognosis; they are definitions of the clinical status built exclusively upon the past performance of the patient; they do not—and are not intended to—convey a medical opinion of the patient's future chances. Incidentally, unintentionally and by circumstantial evidence, there is in some patients some relation between past and future performance; between history and present clinical condition on one hand, and prognosis on the other. But there can be hardly any doubt that many patients with quiescent minimal disease have a better prognosis than many apparently cured patients with far advanced bilateral lesions.

For all practical purposes, physicians force non-medical rehabilitation workers to draw prognostic conclusions from terms in whose definition no prognostic thought has entered. It is the responsibility of the medical profession to create, in coöperation with rehabilitation workers, prognostic terms that have an unequivocal meaning for physician and rehabilitation worker alike. These terms must be developed much *de novo*. Let us hope that the terminology which will eventually be agreed upon by the two groups of workers will be free of the gobblydegonk which has so lustily sprouted in some of the writings in the field of rehabilitation. Even with our tenuous knowledge of prognosis, we must get ready to put it at the service of the non-medical rehabilitation worker, rather than expect him, who is still less equipped to do so than the physician is, to estimate prognosis from past developments and present status. It is hoped that the present Committee on Diagnostic Standards will consider this problem.

Since the publication of Kuthy and Wolff-Eisner's book *Die Prognosenstellung bei der Lungentuberkulose* (pp. xvi + 572, Urban and Schwarzenberg, Berlin and Wien, 1914) and the recognition of the prognostic significance of cavities in the early twenties, little has appeared in the literature on prognosis. But with the realization that intelligent rehabilitation presupposes intelligent medical prognosis, our total knowledge must be reoriented and reassembled under this particular point of view. It does not seem promising that some simple short-cuts in the form of certain tests, such as sedimentation rate, other tests for the colloidal instability of plasma proteins, serological reactions, single

blood counts, blood-chemical findings, tuberculin test or even roentgenological findings *per se*, will be judged to be prognostically indicative; it is more likely that prognosis must be derived from the total clinical picture, from which sound judgment must derive an estimate with proper consideration of the less tangible factors of constitution, socio-economic conditions and personality aspects of a psychic nature.

MAX PINNER

AMERICAN TRUDEAU SOCIETY
The Streptomycin-Tuberculosis Research Project
H. McLEOD RIGGINS¹ AND H. CORWIN HINSHAW²

The Committee on Therapy of the American Trudeau Society has closely observed all developments in drug therapy of tuberculosis during the past several years. The group has made detailed studies of results achieved by various investigators with drugs such as promin and diasone, and more recently streptomycin. It is suggested that persons interested in this field might choose to review the reports of this Committee which have been published from time to time in the *AMERICAN REVIEW OF TUBERCULOSIS*.

When it appeared in January, 1946 that streptomycin had real therapeutic potentialities in the treatment of tuberculosis, the Committee reviewed all cases which had been treated up to that time and issued a report of their findings.³

In the autumn of 1946 the manufacturers of streptomycin were able to produce a sufficient amount of the drug to permit expansion of clinical research. They donated a generous amount of the drug to the American Trudeau Society, sufficient to treat approximately 250 cases of pulmonary tuberculosis. We are also pleased to report that, at this writing, the streptomycin producers are apparently favorably considering making an additional donation of streptomycin to the Society at an early date. If more of the drug is donated, the present research project will be continued at least at the present level; and, should funds from the Research Grants Division of the U. S. Public Health Service become available after July 1, 1947, the project could be considerably expanded to include additional investigators and various types of extrapulmonary tuberculosis. At the present writing, only cases of pulmonary tuberculosis are being studied under the auspices of this Committee. Expansion and broadening of the program are highly desirable in order to determine the therapeutic potentialities of streptomycin in different types of tuberculosis, and also its limitations and possible toxic effects under different regimens of administration. Following the donation of streptomycin to the Society, the Executive Committee selected a group of eight investigators⁴ in different parts of the country, qualified by training and experience, and having a special interest in clinical research in tuberculosis. These investigators were charged with the responsibility of carrying out therapeutic trials with streptomycin in order to determine the usefulness and limitations of the drug in the treatment of pulmonary tuberculosis.

¹ President, American Trudeau Society. Address: 140 East 54th Street, New York, New York.

² Chairman, Therapy and Streptomycin Committees, American Trudeau Society. Address: Division of Medicine, Mayo Clinic, Rochester, Minnesota.

³ *Am. Rev. Tuberc.*, October-November, 1946, 54, pages 439-443.

⁴ Dr. H. Corwin Hinshaw, Dr. J. Burns Amberson, Dr. Emil Bogen, Dr. Kirby Howlett, Dr. Walsh McDermott, Dr. E. N. Packard, Dr. H. McLeod Riggins and Dr. H. Stuart Willis.

At the direction of the Executive Committee of the Society, the President appointed the directors of the eight clinical research projects to a Clinical Streptomycin Committee which has met at regular intervals to insure uniform criteria for selection of patients, minimum clinical and roentgenological standards and to exchange information with regard to results observed concerning the toxic potentialities of the drug, optimum dosage, methods and duration of treatment and other clinical problems which are constantly arising.

It is important to emphasize that this constitutes a closely integrated series of projects which are, in many respects, unique in clinical research. This makes possible the prepublication confirmation of findings by various investigators and the free interchange of information by the investigators to their constant mutual advantage.

In order to insure the best possible correlation of the laboratory and clinical phases and problems of the research project, the President also appointed a Laboratory Committee on Streptomycin⁵ with representatives from the Medical Research Committee of the National Tuberculosis Association and the Committee on Laboratory Procedures of the Trudeau Society.

The research project got under way in November, 1946, and has been closely correlated with similar studies being carried on by the Veterans Administration, the Medical Services of the Army and Navy and with work initiated three years ago at the Mayo Foundation and Clinic, and during the past year at New York Hospital, Cornell University Medical School.

Following the donation of streptomycin to the Society, it was realized that considerable funds would be necessary to carry out the research studies. Accordingly, the problem was placed before the Executive Committee of the National Tuberculosis Association. The National Association immediately allocated funds for the necessary committee activities, and in addition, made a generous contribution toward implementing the research project.

It was learned that the Tuberculosis Control and the Research Grants Divisions of the U. S. Public Health Service were interested in further research on streptomycin in the treatment of tuberculosis. Conferences were held between representatives of these two divisions, the National Tuberculosis Association and the American Trudeau Society. As a result, early in 1947 the Research Grants Division placed \$100,000 at the disposal of the Society for the initiation of this project. About this time, Surgeon General Parran of the U. S. Public Health Service appointed a Tuberculosis Study Section composed of investigators representing different fields of tuberculosis research.

The American Trudeau Society and the Tuberculosis Study Section are working in close harmony. Some of the major and more immediate objectives of the two groups are:

1. Controlled clinical studies to determine further the usefulness and limitations of streptomycin in the treatment of tuberculosis when given alone or in combination with some other antibacterial agent.

⁵ Dr. H. Stuart Willis and Dr. Guy P. Youmans, Co-chairmen; Dr. Emil Bogen, Dr. H. Corwin Hinshaw, Mr. William Steenken, Jr. and Dr. C. Eugene Woodruff.

2. To investigate certain bacteriological problems, including the tendency of tubercle bacilli to become resistant to streptomycin during or following treatment; and the incidence, degree and duration of drug resistance.
3. To determine whether or not increased resistance to streptomycin alters the virulence of tubercle bacilli.
4. To study the virulence of tubercle bacilli which do not become resistant to streptomycin following drug therapy. Many other bacteriological problems are also to be investigated.
5. Further animal experiments are to be undertaken.
6. Studies of human and animal pathology following treatment with streptomycin are to be continued and expanded with the hope of throwing additional light on many obscure problems, such as the effect of streptomycin on the vestibular apparatus and the eighth nerve, and also, if possible, to determine the mechanism by which streptomycin "suppresses" the growth of tubercle bacilli *in vitro* and *in vivo*.

7. One of us (H. M. R.) believes that clinical and roentgenological relapse of the disease following remissions induced by streptomycin would seem to suggest that certain specific immunological forces may become depressed under the influence of the antibiotic, temporarily or possibly for indefinite periods of time. Also, perhaps certain strains of tubercle bacilli with which the immunological forces of the host are comparatively less able to cope, gain ascendancy, possibly as a result of the "suppressive" action of streptomycin and the consequent dying off of other strains of tubercle bacilli. To test this hypothesis, studies should be devised and carried out in an attempt to: (1) evaluate the changing resistance on the part of the host during streptomycin treatment, more especially during periods of drug remission, and relapse of the disease; (2) determine, if possible, what if any demonstrable biological or biochemical changes may occur in tubercle bacilli as a result of their having lived and reproduced in a different (streptomycin) environment.

These and other physiological, bacteriological, pathological, immunological and clinical problems have already become manifest and will require most careful, coördinated and coöperative studies if we are to realize the best returns of our combined efforts.

In order to insure adequate laboratory facilities, uniform and minimum laboratory standards and procedures, three Central or District Laboratories and their directors were designated. These are: (1) Trudeau Sanatorium, Trudeau, New York, Mr. William Steenken, Jr., Director; (2) Northwestern University Medical School, Chicago, Illinois, Dr. Guy Youmans, Director; and (3) Olive View Sanatorium, Olive View, California, Dr. Emil Bogen, Director. Each of these three laboratories has received \$25,000 from the Research Grants Division. In addition to certain routine laboratory work, these District Laboratories have agreed to:

1. Aid in the training of laboratory technicians, especially in regard to sensitivity studies of tubercle bacilli to streptomycin.

2. To investigate special bacteriological and laboratory problems which may arise.

3. To test cultures of tubercle bacilli which have been found resistant to streptomycin by local laboratories.

4. To serve as consultants to the clinical investigators and their laboratories regarding any pertinent bacteriological or laboratory problems and procedures.

5. To conduct basic research in tuberculosis.

This arrangement not only provides for minimum laboratory standards, but relates the laboratory and clinical phases of the research program in the closest possible way.

Joint meetings of the Laboratory and Clinical Streptomycin Committees further insure close correlation of the clinical and laboratory phases of the work.

It is believed that adequate machinery has been set up to correlate and coordinate the studies being carried on by the various groups, that is, the American Trudeau Society, the Tuberculosis Study Section of the U. S. Public Health Service, the Veterans Administration and the Medical Services of the U. S. Army and Navy. Every effort will be made to relate continually the laboratory and fundamental pathological and physiological research studies to the clinical studies. It is felt that a great deal of information regarding the therapeutic and toxic properties of streptomycin in the treatment of tuberculosis has already been obtained, but it is realized that it is highly desirable that additional research studies be carried out as indicated.

On the basis of information available at the present time from all possible sources, the following conclusions appear to be warranted:

1. Streptomycin exerts unprecedented therapeutic effects upon well-established experimental tuberculosis in guinea pigs. Under some conditions it is possible to eradicate the disease in a considerable proportion of animals, even though the disease had been permitted to develop to an advanced stage prior to institution of treatment.

2. Streptomycin is the first antibacterial drug which has shown definitely promising results in the treatment of certain types of pulmonary and extrapulmonary tuberculosis in man.

3. Under certain circumstances, streptomycin appears to lessen or to prevent further multiplication of tubercle bacilli in lesions of human tuberculosis, but usually this suppressive effect is of limited duration. After a few weeks or months of continuous treatment, streptomycin resistant tubercle bacilli may appear and fail to yield to streptomycin therapy. Fortunately, there are types of tuberculosis in which it appears that only temporary suppression of the infection is necessary in order to permit natural defensive mechanisms to gain ascendancy. Streptomycin, like sulfa drugs and penicillin, suppresses disease-producing bacteria; their eventual eradication being dependent upon immunological mechanisms of the host.

4. During its period of effective action, streptomycin administration frequently results in marked amelioration of symptoms of pulmonary tuberculosis, in-

cluding reduction in cough and expectoration, reduction in fever, return of normal appetite and sense of well-being.

5. In the highly fatal types of generalized tuberculosis, including miliary tuberculosis and tuberculous meningitis, streptomycin frequently brings about a striking clinical, roentgenographic and bacteriological remission. Unfortunately, this state of remission may continue for only a few months, but a small number of cases of otherwise fatal tuberculous meningitis have remained well for more than a year without evidence of recurrence of their disease. It is now widely believed that treatment with streptomycin is mandatory in early cases of miliary tuberculosis and tuberculous meningitis. This makes it imperative that funds for purchase of streptomycin be made readily available for emergency treatment of such cases.

6. Marked improvement has frequently been noted in previously progressive cases of ulcerating tuberculosis involving the larynx, the trachea and the larger bronchi.

7. Chronic, long-standing tuberculous lesions involving lymph nodes, the thoracic wall, etc. with sinus tracts, which have drained pus for months or years, frequently subside within a few weeks following streptomycin treatment. Some of these may recur.

8. Tuberculosis of the kidneys and bladder has not been fully studied, but results are less encouraging than in the types of disease mentioned above. Symptomatic improvement has frequently been observed but actual arrest of the disease is exceptional.

9. Tuberculosis of the bones and joints, of the intestinal tract, of the peritoneal cavity, of the skin, of the eye and other relatively infrequent types of the disease have not been adequately studied to justify even tentative conclusions as yet. Early reports have been encouraging in some of these cases.

10. Streptomycin has definite toxic potentialities which must be considered constantly. These hazards must be compared with the hazards of the disease under treatment.

11. The toxic reaction most frequently encountered is a disturbance of equilibrium, which is uncomfortable but usually not dangerous. In most instances it has been extremely mild and in a few it has been severe. In all instances, a satisfactory degree of recovery or compensation to this symptom has occurred. Smaller doses of the drug produce less severe vestibular disturbances than larger doses. Deafness has been known to occur, but nearly all such instances have been in patients with tuberculous meningitis and probably would not have occurred but for the necessity of continued treatment in high dosage without interruption due to the otherwise fatal nature of the disease. The danger of deafness is not great when patients are properly observed in sanatoria and hospitals staffed by physicians who are familiar with the use of streptomycin. Statements that blindness has occurred due to streptomycin toxicity have not been verified. Streptomycin has frequently produced mild irritation of the kidneys, but it is believed that serious renal damage can be avoided.

12. The toxicity of streptomycin now appears to be sufficiently great to deny

use of the drug to those patients who are making satisfactory progress under conventional forms of treatment. At present, most experienced physicians prefer to reserve the limited supply for patients more acutely ill, and especially for those in whom the disease has been progressive during recent months, and no other treatment is likely to be effective. Streptomycin is of no lasting or significant benefit to patients who apparently have hopeless, destructive types of pulmonary tuberculosis.

13. A great deal remains to be learned in regard to how streptomycin may be employed more effectively. The optimum dosage schedules have not yet been determined and the maximum duration of treatment is not definitely known. There is considerable evidence to suggest that often marked symptomatic and definite roentgenographic and bacteriological improvement may follow the administration of smaller doses of streptomycin than generally used heretofore. One to two grams daily, given for periods of 42 to 120 days, depending in part on whether or not the organisms become drug resistant, may bring about remission of the disease. Toxic manifestations seem to be less frequent and severe when smaller doses are given. Whether or not smaller doses given for shorter periods of time may cause drug resistance to develop less rapidly and possibly to a lesser degree is still unknown and is under investigation. Intermittent treatment, that is, every other day, every other week or every other fortnight is also being investigated to determine (1) whether the therapeutic effect of such regimens is adequate, (2) whether such regimens are likely to cause less toxemia. Many possibilities for improving the efficacy of the antibiotic in reducing its toxic potentialities have not as yet been fully explored.

14. It should be emphasized that streptomycin should be regarded as an adjunct to the conventional and effective methods of tuberculosis therapy which are now widely used. Antibiotic therapy is not likely to replace surgery, except in rare instances, but may increase the safety of thoracic surgery and make it available to a larger number of patients. The prevention of tuberculosis by means of improved living and working conditions and health education, early diagnosis, and prompt and adequate sanatorium or hospital care remain the most effective methods of controlling tuberculosis.

Those possessing adequate clinical, roentgenological and laboratory facilities, and who are properly qualified by training and experience and have some interest in tuberculosis research are encouraged to write to the Executive Secretary of the American Trudeau Society, 1790 Broadway, New York City, or to the Executive Secretary of the Tuberculosis Study Section, U. S. Public Health Service, Bethesda, Maryland for further information regarding research projects being sponsored by the two groups.

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Actinomycosis.—Infections in man due to the aerobic, partially acid-fast *Nocardia asteroides* are rare as compared to those due to the anaerobic *Actinomyces bovis*. The symptoms, course of the disease and response to therapy are so nearly alike that the disease produced by the two types of fungi should be called actinomycosis. Thirty-two cases of infection with *N. asteroides* have been collected from the literature. The mortality rate appears to be high: 28 of 32 patients were dead at the time the reports were published. The infection was pulmonary in 28 cases, and the brain was the site of metastasis in at least 10. In 2 cases infection of the lungs and the chest wall was apparently cured by surgical drainage, sulfonamide therapy, iodides and roentgen therapy. Two new cases of infection with *N. asteroides* are added in this report. The first was a man of 63, who was hospitalized for three and a half months for cough, sputum, loss of weight and pulmonary disease. He responded well to trials of sulfadiazine therapy, but the etiological agent was not recognized until late, when the fungus was isolated from his sputum, subcutaneous abscesses and blood stream. At autopsy the lungs, peribronchial lymph nodes, heart, thyroid, kidneys, spleen, intestines, muscles and subcutaneous tissues contained abscesses produced by *N. asteroides*. The second case was that of a woman of 49, who was hospitalized for five days prior to death with a clinical diagnosis of an intracranial lesion without localizing signs. Autopsy revealed an abscess in the cerebellum caused by *N. asteroides*. The lungs are suspected as the primary focus, and no other metastases were found.—*Actinomycosis*

Due to Nocardia Asteroides, W. M. M. Kirby & J. B. McNaught, with the technical assistance of G. S. Reeves, *Arch. Int. Med.*, November, 1946, 78: 578.—(G. C. Leiner)

Loeffler's Syndrome.—Pulmonary infiltrations with eosinophilia have been reported in association with trichinosis, chronic brucellosis, amebiasis and infestation with *Necator*, *Faciola hepatica*, *Asearis* and *Strongyloides*. Two cases are presented to emphasize the fact that eosinophilia associated with pulmonary infiltrations may occur in coccidioidomycosis. The first patient developed fever, pulmonary infiltrations and an eosinophilia as high as 89 per cent. Subsequently adenopathy and pustules on the extremities and scalp appeared. Skin tests for coccidioidomycosis were positive, and biopsy revealed coccidioidomycosis. Clinical improvement, including decrease in pulmonary infiltrations, sedimentation rate and eosinophilia, followed treatment with "ball-mill coccidioides vaccine." The second patient complained of fever, sore throat, cough and, subsequently, developed pulmonary infiltration accompanied by enlargement of the mediastinal lymph nodes. The skin tests, complement fixation and precipitin tests were positive for coccidioidal infection. The eosinophilia improved with the clearing of the pulmonary infiltrations and the patient's blood count gradually returned to normal. The pulmonary infiltrations were present for sixty-seven days in the one case and forty-six days in the second.—*Pulmonary Infiltrations with Associated Eosinophilia*, F. M. Willett & E. Oppenheim, *Am. J. M. Sc.*, November, 1946, 212: 608.—(G. F. Mitchell)

Pleuropulmonary Tularemia.—The effect of streptomycin therapy in 12 cases of pleuropulmonary tularemia was studied; an additional 3 cases were seen but not treated with streptomycin. In 8 of the 12 patients there was no history or physical evidence of a primary skin lesion. The commonly employed clinical division of tularemia with emphasis on portal of entry (ulcero-glandular, oculo-glandular) is considered somewhat arbitrary. In 2 patients, the possibility of infection through the ingestion of infected meat was suggested by the presence of pharyngeal ulcers and diarrhea. Five patients gave a history of contact with wood or dog ticks. This emphasizes the previously demonstrated fact that tularemia may be acquired by means other than the handling of infected tissues. Ten had bronchopneumonia and in 5 of these pleural effusions were demonstrated. There was one instance of additional acute pericarditis and one of pleural effusion with no demonstrable pneumonia. Diagnosis was based on a rising serum agglutinin titer against *P. tularensis* and, in 7 cases, by the isolation of the organism by animal inoculation. All of the patients responded to treatment in a remarkable manner. Fever usually declined within twenty-four hours and clinical improvement occurred even before decline of temperature to normal values. One patient died suddenly after apparent recovery; death was believed to be due to massive pulmonary embolism. Seven patients have been followed at intervals of from one to five months and have remained well. Animal inoculation of sputum and pleural fluid after therapy indicated that streptomycin resulted in a rapid elimination of the organism. Complete healing of lesions was comparatively slow and usually took several weeks. There was a rise in the serum agglutinin titer in all patients during or after treatment. This would seem to indicate that early treatment with the antibiotic does not prevent the development of acquired immunity. The drug was administered intramuscularly at four hour intervals in daily dosages ranging from 0.5 to 1.0 g. No relapses have been observed. These dosages are comparatively small and

larger amounts are probably advisable in view of the possibility of the development of resistant organisms, although this was not observed in this series. Tularemia is often difficult to diagnose in the early stages in view of the late development of agglutinins. Isolation of the organism is hazardous and four to seven days may elapse before the animal dies. The author feels that streptomycin should be used early as a therapeutic test in any suspicious case even before the diagnosis is confirmed. Two days of treatment is usually sufficient to judge the response. The full course of treatment in this series ranged from five to nine days.—*Pleuropulmonary Tularemia: Observations on 12 Cases Treated with Streptomycin*, J. S. Hunt, *Ann. Int. Med.*, February, 1947, 26: 263.—(H. R. Nayer)

Atypical Pneumonia.—In the established case, the roentgen opacity is homogeneous and translucent; early changes cause blurring of the bronchopulmonary markings; resolution is almost in reverse order, structural intensification being the last sign of previous parenchymal infiltration to disappear. By the routine use of the appropriate lateral projection of the chest in conjunction with the conventional film, it has been abundantly demonstrated that the infiltration of atypical pneumonia is segmental in type, the distribution being closely related to the zones supplied by the secondary branches of the bronchial tree. That the disease is one of bronchogenic origin is further attested by the frequency of minimal atelectasis and followed infrequently by secondary infection and bronchiectasis. The intralobar septa probably serve as limiting boundaries to the characteristic interstitial reaction. The disease should be considered as a confluent lobular pneumonia of segmental distribution.—*Primary Atypical Pneumonia*, W. E. Cryslar, *Am. J. Roentgenol.*, September, 1946, 56: 324.—(J. E. Farber)

Posttraumatic Pneumonia.—Posttraumatic pneumonia is defined as the type of pneumonia which follows trauma to the chest with the exception of pneumonias following penetrating

chest wounds. The pathogenesis of post-traumatic pneumonia is a vagal reflex causing spasm of the bronchial tree and bronchial hypersecretion resulting in pulmonary atelectasis. Of 73 patients with posttraumatic pneumonia, 28 had an intact thorax and 45 had fractures of the thoracic cage. There are three types of pulmonary injuries: those due to direct violence, to *contrecoup* and to 'pincer' forces in V-shaped spaces. The lesion occurring most commonly after direct violence is contusion of the parietal pleura. The lung below the incoming ribs may show varying degrees of subpleural ecchymosis. The typical *contrecoup* lesion is posterior. It consists of a hemorrhagic straight line corresponding to the angles of the ribs. The lesion due to pincer forces consists of contusion of the structures in the costophrenic angle caused by nipping of the lung between the lateral wall of the chest and the spleen or the liver. Cavity formation is common in extensive contusions, subpleural blebs are common in aircraft accidents. Traumatic pulmonary lesions at the onset of the pneumonia were more often present in patients with fractures of the thoracic cage. They were in order of frequency: contusion of the lung, hemothorax, pneumothorax, hemopneumothorax, subcutaneous emphysema and mediastinal emphysema. In 92 per cent of the patients pneumonia developed within six days of the injury. In 54 patients pneumonia developed only on the same side as the injury. Nine patients had bilateral pneumonia and 10 patients developed pneumonia on the *contrecoup* side only. The course and complications of posttraumatic pneumonia simulate those of mild to moderately severe primary pneumococcic pneumonia. Posttraumatic pneumonia can be prevented or minimized by the early treatment of all patients with injury to the chest for pulmonary atelectasis and potential infection. The intravenous administration of 0.0004 g. of atropine and of 0.03 g. of papaverine every four hours for two days after injury will relieve bronchospasm and hypersecretion. Prophylactic chemotherapy is indicated. Once post-traumatic pneumonia has developed chemo-

therapy should be intensified. Pleuritic pain should be relieved by local anesthesia. Expectorants, oxygen by inhalation have to be used as indicated.—*Pneumonia following Non-penetrating Pulmonary Injuries*, E. Phillips, J. A. M. A., January 18, 1947, 133: 161.—(H. Abels)

Lipiodol Pneumonia.—Three cases of bilateral basal pneumonia are reported, associated with urticaria and eosinophilia following the intrabronchial instillation of lipiodol. The importance of skin testing individuals with allergic backgrounds is stressed.—*A Pulmonary Reaction following Intrabronchial Instillation of Lipiodol in Bronchial Asthma*, S. I. Kooperstein & H. E. Bass, Am. J. Roentgenol., November, 1946, 56: 569.—(J. E. Farber)

Pneumonia with Erythema Multiforme Exudativum.—Six cases of erythema multiforme exudativum with involvement of the mucous membranes were seen. Of these, 3 developed pneumonia. The cause of the disease is unknown. Blood, throat washings, vesicle fluid and material from the lung of a fatal case were injected into various animals and embryonated hen's eggs; no information as to the etiology of the disease was obtained. Pneumonia occurs probably more often in this disease than has been recognized. The pneumonia in these 3 cases was similar to primary atypical pneumonia. In 2 of the 3 cases cold hemagglutinins were found. In 2 of the 3 cases without pneumonia the same tests were made and were found negative.—*Association of Pneumonia with Erythema Multiforme Exudativum*, Commission on Acute Respiratory Diseases, Fort Bragg, N. C., Arch. Int. Med., December, 1946, 78: 687.—(G. C. Leiner)

Mustard Gas Bronchitis.—Persons employed in the handling of mustard gas and exposed to small quantities of the gas over a prolonged period of time may sustain damage to the respiratory tract which may leave them partially or totally disabled. The authors studied 200 patients who, during their work in

an industrial plant, developed acute and chronic symptoms following exposure to mustard gas. Symptoms came on within three weeks to twelve months after onset of exposure. There are symptoms of irritation of the conjunctival and respiratory mucous membranes associated with dysphagia, anorexia, vomiting and weight loss. Symptoms improve following removal from the environment only to recur when the patient returns to the same work. After a number of episodes, it is necessary to remove the worker permanently from exposure to the gas. Residual symptoms persist in a considerable number; they are persistent hacking cough, wheezing and chest tightness most marked during damp weather. Such patients are hypersensitive to fumes or dust of any kind and may develop dyspnea on exertion to such a degree that they cannot perform any arduous labor. Roentgen findings range from minimal increase in bronchovascular markings to definite peribronchial thickening and patchy basal pneumonitis. Fifty-five out of 85 patients on whom lipiodol studies were done showed evidence of bronchiectasis ranging from minimal to extensive involvement of four lobes. The sedimentation rate is normal or slightly elevated; vital capacity is somewhat diminished. Diagnosis is based mainly on history and clinical findings. Treatment consists of removal from contact with fumes and dust, postural drainage, high fluid intake and expectorants. The effects of nebulized penicillin are being studied.—*Residual Mustard Gas Bronchitis: Effects of Prolonged Exposure to Low Concentrations of Mustard Gas*, P. Morgenstern, F. R. Koss & W. W. Alexander, *Ann. Int. Med.*, January, 1947, 26: 27.—(H. R. Nayer)

Dextrocardia and Bronchiectasis.—Dextrocardia, secondary to fibrosis and retraction of the right lung has been known to occur both in fibroid tuberculosis and with bronchiectasis. The author reports such a case in association with the latter condition.—*Simulated Dextrocardia Associated with Bronchiectasis*, S. A. Leader, *Am. J. Roentgenol.*, December, 1946, 56: 748.—(J. E. Farber)

Bronchiectasis.—The authors summarize their experience in the treatment of 390 patients with bronchiectasis. Pulmonary resection is the only permanent cure for this condition. Two hundred and twenty lobectomies were performed with only one death. In 5 patients, pneumonectomy was performed for disease involving the entire lung. Drainage, both postural and bronchoscopic, and various methods used in combating infection, including penicillin, are valuable as palliative and preoperative therapy. Patients who evidence only roentgen evidence of bronchiectasis and those who have only minimal symptoms are treated conservatively; those with disease of all five lobes are obviously too far advanced for radical cure. In the absence of any other medical contraindication, lobectomy is recommended for all other patients. As long as the right upper lobe and the upper aspect of the left upper lobe are free of disease and the cardio-respiratory reserve is adequate, bilateral resection should be considered. Where all the diseased tissue cannot be removed, removal of the more advanced bronchiectasis has resulted in considerable improvement. Preoperative studies should include bronchograms outlining all five lobes, bronchoscopy and bronchspirometric studies. A period of at least four to six weeks should elapse following bronchiography to allow elimination of the oil to avoid postoperative pneumonitis. A one- to two-week course of intratracheal penicillin is valuable in patients with copious sputum. The operations have been done by individual ligation technique. In patients with copious sputum, early operative occlusion of the bronchus is important in preventing aspiration into the opposite lung. All pleuritic adhesions between the upper lobe and the chest wall are severed to permit adequate compensatory expansion. Closed intercostal drainage is maintained for forty-eight hours to permit effective drainage of serum and air. Bronchoscopic aspiration is performed on all patients immediately postoperatively. Temporary phrenic nerve paralysis is produced where high lingulectomy or middle lobe lobectomy is performed in combination with

removal of the lower lobes. Bronchospirometric studies performed on 26 patients postoperatively demonstrated that the function of the remaining pulmonary tissue on the operated side is dependent largely on the postoperative pleural reaction. Studies of function before and operation in a small group demonstrated that oxygen consumption and ventilation several months postoperatively were either slightly below normal values, or essentially the same or even improved over preoperative values. The latter effect illustrates the fact that blood flowing through bronchiectatic lobes is often inadequately oxygenated; when the diseased lobe is removed, blood can then only be circulated through alveoli that allow proper oxygenation.—*Surgical Treatment of Bronchiectasis*, E. B. Kay, R. H. Mcade, Jr. & F. A. Hughes, Jr., *Ann. Int. Med.*, January, 1947, 26: 1.—(H. R. Nayer)

Aerosol Penicillin.—This procedure used preoperatively caused a marked decrease in the amount of sputum, thus giving better assurance of a good anesthetic course. The patient was judged a good risk if he had no sputum after aerosol therapy for two weeks or the sputum was reduced to a small volume and remained so. The sputum of the different types responded in the following order; most rapid for tubular bronchiectasis, next for sacular bronchiectasis or an abscess cavity, and slowest for the cases with associated bronchial obstruction and atelectasis. Both cough and accompanying bronchitis were markedly improved. Concomitantly, postural drainage, bed-rest, raising of blood hemoglobin and proteins to normal levels, intramuscular penicillin and sulfadiazine should be used. Individualization of treatment is important. Pathological change must be evaluated fully so that duration and type of treatment can be tentatively prognosticated and outlined. Children are hard to evaluate as they may swallow sputum, and it is difficult to be sure that they take inhalation therapy efficaciously. Adults showed a uniformly good response to aerosol therapy and anesthetic courses were without complications.—*Aerosol Penicillin as a Thera-*

peutic Adjunct in the Preparation of Patients with Suppuration of the Lung for Pulmonary Resection, C. W. Findlay & R. H. Sweet, *J. Thoracic Surg.*, February, 1947, 16: 81.—(J. H. Cope)

Interlobar Empyema.—This condition is a complication of pneumonia, metastatic infections, lung abscess or trauma and may occur as a primary infection. The characteristic history is pain on the affected side, fever, cough and dyspnea. Foul sputum may occur later in the disease and indicates rupture of the empyema into a bronchus. X-ray films in the anteroposterior and lateral views will localize the abnormal density in the interlobar fissure. Treatment is surgical.—*Interlobar Empyema*, J. Lérutin, *Am. J. Roentgenol.*, August, 1946, 56: 156.—(J. E. Farber)

Atelectasis after Surgery.—Airlessness of a part of all of a lobe or lung is a common postoperative complication. Evidence to allow its differential diagnosis did not appear until between 1914 and 1930. Complete bronchial obstruction is the one mandatory factor for its production; all others are predisposing or favoring factors. Bronchial obstruction may be produced in three ways: reflex bronchospasm, swelling of the bronchial mucosa, or a plug of secretions or aspirated material. The first two modes are rare, but the third is common. A viscid plug of mucus, which is allowed to remain because of hypoventilation, or not expelled by the cough reflex, ciliary action or bronchial peristalsis, is the major factor. The numerous factors which may predispose to atelectasis can be classed in two groups: (1) factors associated with hypoventilation (including location and type of operation, elevation of diaphragm, reduced excursion of diaphragm, lowered vital capacity, increased intrapleural pressure, air beneath the diaphragm, severity of operation, amount of postoperative pain, muscle spasm and splinting, obesity, intraabdominal complications, abdominal binders, sedatives and hypnotics before and after operation, posture, old age, debilitating conditions, poor operative risks,

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- sex, straining respirations, anesthesia and surgical technique); (2) factors associated with the formation of bronchial plugs (including preëxistent pulmonary disease, hypersecretion of saliva and tracheobronchial mucus, preoperative use of atropine, aspiration of material from the mouth, pharynx and nasopharynx and ineffective cough). Operations on the abdomen, especially in the upper part, cause hypoventilation in proportion to the severity of the operation and the amount of vital capacity, as does an abdominal binder. Opiates and barbiturates decrease pulmonary ventilation, and opiates depress the cough reflex and ciliary action (a dangerous action in smoker's bronchitis). Most static positions embarrass the ease of breathing. The male sex is the more susceptible to atelectasis, because of the tendency to abdominal type of breathing. Inhalation anesthesia (spinal anesthesia is a more common cause) acts by diminishing body tonus. A specific irritating effect of cyclopropane is disputed. The incidence of respiratory complications varies directly with the depth and duration of anesthesia. The lungs should be ventilated with air after anaesthesia, since oxygen, carbon dioxide and anesthetic gases are absorbed much faster from the alveoli than air. Preoperative pulmonary inflammation is not a necessity for the production of collapse, but of atropine is uncertain; it is possibly beneficial. Careful anesthetic and surgical technique decrease the hazard to the lungs. Aspiration of material from the upper respiratory tract is a most important factor in obstruction and atelectasis. When obstruction has occurred, the plug must be expelled by cough or evacuated by bronchoscopy. If this is not possible, the fate of the lung tissue depends on the type of bacteria present. Pneumococcus, if the bacteria are virulent, they may cause a pneumonia. Certain organisms from the mouth may cause lung abscess.—*The Pathogenesis of Postoperative Atelectasis*, C. J. Ved-
- renne, *New Orleans M. & S. J.*, November, 1946, 99: 220.—(W. H. Oatway, Jr.)
- Middle Lobe Atelectasis.**—Atelectasis of the middle lobe occurs more often than atelectasis of other lobes because of the peculiar anatomy of the middle lobe bronchus. This bronchus is relatively narrow; it leaves the main bronchus at an acute angle; therefore, the bronchus is easily compressed or kinked by lymph nodes near its origin. In the upper and lower lobes usually smaller bronchial branches only are affected and atelectasis of small central parts of the lung results. The comparatively frequent stenosis of the middle lobe bronchus produces atelectasis of the entire middle lobe. Secondary inflammation behind the stenosis resulting in induration with or without bronchiectasis is common. Two cases of middle lobe atelectasis caused by calcified lymph nodes are described. In the last few years bronchial stenosis due to large lymph nodes has been seen frequently in adults, possibly due to the poor nutrition and living conditions of the population.—*Der Mittellappen als Punctum minoris resistentiae der Lunge*, E. Zdansky, *Wien. klin. Wchnschr.*, April 19, 1946, 58: 197.—(G. C. Leiner)
- Silicosis in Metalliferous Mining.**—The decennial supplement of the Registrar General of England reveals that the occupation with the highest standardized mortality ratio among males 20 to 65 is "tin and copper mining below ground." The third highest is "other metalliferous mining below ground," and the fifth is "slate mining and quarrying." The development of silicosis is often insidious, but the onset of symptoms is often abrupt. The immediate cause of death is often congestive heart failure or bronchopneumonia. During the past fifteen years, medical supervision under the direction of Caw has been carried out in the hematite miners in Cumberland, with great success. He claims that no miner who has entered the mines in that period has developed any signs of dust diseases of the lungs. This has been achieved by careful

selection of the men, repeated examination and routine chest skiagraphy. Early cases of tuberculosis are identified and removed.—*Silicosis and Metalliferous Mining in England, Brit. M. J., November 16, 1946, 4480: 743.*—(R. W. Clarke)

Pneumoconiosis.—The study includes the results of many hundreds of clinical examinations and of 592 necropsies of certified silicotics among South Wales anthracite miners. Slighter grades of the disease often produce no symptoms. The chief symptom is dyspnea of gradual development. Cough is variable and is often absent in uncomplicated cases. Sputum is slight or absent. Black "spit" indicates the presence of breaking-down pulmonary lesions. Pain is absent if there is no pleurisy. Fever and wasting are found only if there is infection. Physical examination often reveals reduced pulmonary expansion, impairment of percussion note, slightly prolonged expiratory sounds and sometimes râles. Symptoms are severe and abnormal physical signs are slight. Necropsy shows the lungs to be adherent, especially the upper lobes, emphysema and areas of black fibrosis, varying from small discrete nodules up to large areas of consolidation. The nodules in those patients exposed to dust with high silica content are harder and more sharply demarcated. The nodules often crumble and excavate; the cavities contain milky black material. The regional nodes are enlarged, fibrotic and anthracotic. Tuberculosis is very frequent among silicotics. It is questionable whether this is so in the pneumoconiosis of hard-coal miners. About 25 per cent of the author's own cases had tuberculosis. This did not include the cases with crumbling which many pathologists regard as tuberculosis. All patients with wasting had crumbling or tuberculosis; the converse was not true. The distribution of lesions was asymmetrical and irregular. Gross bullous emphysema was found in 104 of 230 cases. Pneumothorax was occasionally present. Nontuberculous respiratory affections, chiefly pneumonia, were found in one-

fifth of the cases. Heart failure was the most frequent cause of death. It was manifested by right-sided failure or terminal pulmonary edema. There was only one case of carcinoma. The cause of death was tuberculosis in 26 per cent, nontuberculous respiratory affections in 18 per cent, cardiac failure in 37 per cent and unrelated conditions in 19 per cent. Many patients with advanced silicosis and most patients in the early stage of the disease survived for many years unless they also had tuberculosis. Prevention among workers in hard headings consists of watering everything and of using a ventilating current to remove dust. At the coal face, dust is harder to eliminate. The use of aluminium is not helpful. Tuberculous individuals should be kept out of the mines. There is no special treatment.—*Pneumoconiosis in South Wales Anthracite Miners, C. G. Gooding, Lancet, December 21, 1946, 2: 891.*—(A. G. Cohen)

Disability in Dust Diseases.—The assessment of the amount of disability in dust diseases of the lungs is difficult. No satisfactory method is available. X-ray evidence is inadequate, as illustrated by the nodulation caused by iron oxide in siderosis and that caused by silicosis. Methods such as comparing the lung fields in X-ray films on inspiration and expiration, exercise tests, oxygen content of blood, blood sedimentation rates and vital capacity and residual air have been used. Vital capacity is probably the best guide of the easily performed tests. When the ratio of residual air to total capacity exceeds 40 per cent, some degree of impairment is usually apparent. It is hoped that satisfactory methods for assessment of pulmonary disability in pneumoconiosis will be found.—*Assessment of Disability in Dust Diseases of the Lung, Brit. M. J., August 31, 1946, 4469: 301.*—(R. W. Clarke)

Foreign Body in Lung.—A 31-year-old patient was hit by an exploding mine and a bean-sized particle entered his right lung. An ab-

cess developed. Medical treatment (salvarsan-, alcohol-injections) was ineffective. Under local anesthesia and fluoroscopic control a wooden sliver, measuring 5 by 10 mm., was removed through an opening made at the site of the scar in the second and third intercostal spaces. In a second session, eleven days later, the metal foreign body was removed. A catheter was inserted into the cavity and Monaldi's suction drainage was instituted. Five thousand units of penicillin were instilled through the catheter into the cavity on four successive days. The general condition of the patient improved rapidly.—*Fremdkörperentfernung aus der Lunge*, K. Domokos, Wien. *klin. Wchnschr.*, November 8, 1946, 58: 675.—(G. C. Leiner)

Chest Tumor Registry.—The functions of the registry are outlined: to receive cases in a specific category, to review diagnoses and obtain consultation on the pathology of difficult cases, to process all material so that it will be available for study and research, and to conduct follow-up studies so that histories will be complete. The chest tumor registry is one of 14 sponsored by the National Research Council. Registering cases still allows the surgeon to do as he wishes with cases and case records. His permission is obtained whenever his case report is used. The advantage is that this is a permanent record, not dependent on changing personnel or policies. Operative reports and X-ray films are necessary for registration. Practically all specimens from all thoracic cases from the Army are registered. The Veteran's Service is registering all available cases. The Registry also has available illustrative material such as photographs, drawings and moving pictures of clinical subjects and operative procedures. Information may be secured by contacting the Army Institute of Pathology, Washington 25, D.C.—*The Chest Tumor Registry*, J. E. Ash, *J. Thoracic Surg.*, February, 1947, 16: 12.—(J. H. Cope)

Spread of Neoplastic Cells through Bronchi.—The possibility that tumors may spread by way of the respiratory passages has been re-

ported but there has been no experimental work verifying this assumption. The presence of mucus and the ciliary motion of the lining epithelial cells were believed to preclude such spread. A recent study of viruses in mice necessitated intranasal instillation of material containing cells from lung tumors. Unexpectedly, this resulted in the development of further lung tumors and this finding led to the experiments to be described. A few droplets of a suspension of suitable neoplastic cells were instilled into the nostrils of small groups of healthy young mice under light ether anesthesia. In several instances the instillation was repeated after five to twenty-four hours. All mice were highly susceptible to subcutaneous implantation of the tumor cells. One strain of lung carcinoma, 3 strains of lymphoid leukemia and 2 strains of myeloid leukemia were used. Twenty-five out of 50 of the mice receiving carcinoma cells, 15 of the 17 receiving lymphoid leukemia, and 11 out of 16 receiving myeloid leukemia gave positive "takes". The carcinoma cells produced progressively growing tumors in both lungs, but at time of death metastases were limited to the regional lymph nodes. One strain of malignant lymphocytes produced systemic disease without leaving any mark at the point of entry into the circulation. Leukemic cells of 4 other strains (2 myeloid and 2 lymphoid) produced tumor-like pulmonary infiltrations, with a spread to regional lymph nodes terminating in generalized leukemia. It is apparent that the epithelial surfaces of the respiratory tract are not safe barriers against the dissemination of neoplastic cells.—*Experiments on the Spread of Neoplastic Cells through the Respiratory Passages*, J. Furth, *Am. J. Path.*, November, 1946, 22: 110.—(J. S. Woolley)

Morphology of Lung Carcinoma.—The correlations between clinical manifestations and morphology of pulmonary carcinoma was studied on 26 cases of resection; 25 of these cases were males, almost one-half of them in the age group between 40 and 50 years, and about the same number were heavy smokers.

Cough, chest pain and hemoptysis constituted the most frequent symptoms. The course of illness lasted from two months to three years. The diagnosis was made in most of the cases on the basis of clinical and roentgenological signs; bronchoscopic examination was helpful in the diagnosis of 4 cases, sputum inclusions in 2 cases and aspiration biopsy in one case. Fifteen pneumonectomies were performed, 9 of them for the right lung and 6 for the left lung; in 11 cases lobectomy was done, 9 times on the right side and twice on the left side. A free pleural cavity was found in 14 cases, adhesions were present in 12 cases. The surgical exploration of the hilar lymph nodes showed metastasis in 3 cases out of 9. Circumscribed tumors were observed in 21 cases: on 4 occasions the tumor was found in the parenchyma; in 16 cases it was peripherally located and in one case the site of the tumor was in a main bronchus. Histological examination revealed 4 per cent undifferentiated small cells, 36 per cent adenocarcinomata and 24 per cent epidermoid carcinomata. Trabecular type of carcinoma was found in 12 per cent and atypical carcinoma in 12 per cent. Fourteen patients died within one month after the operation; postmortem examination in 12 of them showed only 2 cases of distant metastasis and one case of invasion of the thoracic wall. Thus the indication for surgery was justified in 75 per cent of the cases; 8 patients died one month to seven months after the intervention; death was due in all to metastasis. Four patients were alive and showed no evidence of metastasis five months to sixteen months after the operation. In June 1946, 2 patients were alive, both for periods longer than two years and neither of them manifested metastasis; one of them had an adenocarcinoma and one an epidermoid cell carcinoma. There was no clear correlation between the apparent onset of the disease and the moment of the resection: surgery performed in apparently early cases often proved to be too late. This is due to the fact that the lapse of time between the real onset of the neoplasm and the first clinical symptoms is unknown. The late results of surgical treat-

ment depend on the location, morphology and histological type of the tumor. The secondary alterations accompanying lung carcinoma are determined by the location and the development of the tumor. The majority of the tumors removed by surgery originated in medium-sized and smaller bronchi. The opinion is expressed that the mass radiography of the chest will reveal a larger number of lung carcinomata amenable to resection.—*Morfología del cancer pulmonar*, J. A. Taiana, *Prensa méd. argent.*, October, 1946, 33: 2051.—(L. Molnar)

Pancoast Tumors.—In 10,209 autopsies done at the Kaiser Franz Joseph Hospital in Vienna between 1933 and 1942, 302 cases (2.9 per cent) of bronchogenic carcinoma were seen; of these, 43 (14.2 per cent) showed localization in the periphery of the lung; 12 of these were found in the apical region. In only 2, the typical symptoms of a Pancoast tumor had been present. In addition to these 2, 5 cases of bronchogenic carcinoma of the upper lobe showed extension of the tumor to the thoracic wall, partly with rib destruction. The symptoms described by Pancoast may also be found in other diseases with localization in the apex, such as metastases of malignant tumors, tumors of the pleura and of the sympathetic ganglia, Hodgkin's disease. The differential diagnosis between Pancoast tumor and tuberculosis is frequently difficult.—*Ueber Lungenspitzenkarzinome und Tumoren der oberen Lungenfurche (Pancoast-Tumoren)*, O. Wichtl, *Wien. klin. Wchnschr.*, May 3, 1946, 58: 228.—(G. C. Leiner)

Bronchial Adenoma.—Dr. Overholt's material since 1933 showed 305 cases of histologically proven carcinoma and 12 cases of bronchial adenoma. Bronchial adenoma thus represented only 3.9 per cent of the carcinomata, but, while only 87 of these latter were considered amenable to surgical treatment, all 12 cases of bronchial adenoma were successfully treated by resection. The ratio between males and females was 3.8 to 1 in the case of carcinoma and 1 to 1 in the case of

bronchial adenoma. In most of these cases there were signs of invasion of the adjacent tissues and in some cases also of the regional lymph nodes. Distant metastases were not observed and the clinical course also supported the belief that these tumors do not represent true malignant tumors. The onset of the disease is insidious. The first symptoms are usually unproductive cough, later followed by dyspnea and abundant hemoptysis. At later stages phenomena of bronchial obstruction dominate the picture. The diagnosis is suggested by the clinical history; occasionally there is roentgenological evidence of the tumor, but the X-ray film most often shows only secondary pulmonary changes. Bronchography reveals filling defect, or bronchiectasis distal to the tumor. Bronchoscopy is the most important diagnostic procedure; biopsy is sometimes dangerous because of the profuse hemorrhage; another set-back of bronchoscopic examination is that the extrabronchial portion of the tumor cannot be seen. The histological picture of bronchial adenoma is characterized by the absence of mitotic figures and by the tendency of the tumor cells to appear in groups. The pathological diagnosis is by no means easy: it sometimes occurred that the same specimen was variously diagnosed by experienced pathologists. Radium therapy, followed by bronchoscopic insertion of radium and electrocoagulation failed to cure one of the patients of this series. Bronchoscopic extirpation of the tumor is dangerous and ineffective. Pulmonary resection, pneumonectomy in 8 cases and lobectomy in 4 cases, proved to be curative in these cases. — *Adenoma bronchial, estudio de 12 casos tratados por resección pulmonar*, F. E. P. Triccerri, L. Langer & E. Naclerio, *Prensa méd. argent.*, November, 1946, 33: 2207.—(L. Molnar)

Pulmonary Adenomatosis.—Multiple adenomata involving four lobes of the lungs in a 56-year-old woman was complicated by repeated attacks of lobar pneumonia, leading to death.—*Pulmonary Adenomatosis Complicated by Lobar Pneumonia*, C. M. Alexander

& Foo Chu, *Arch. Path.*, January, 1947, 43: 92.—(E. Bogen)

Primary Lung Cancer.—A brief review and plea for early diagnosis and pneumonectomy. — *Le cancer primitif du poumon*, R. Desmoules, *Laval méd.*, January, 1947, 12: 58.—(E. Bogen)

Chylothorax.—A case of traumatic chylothorax is described. A soldier developed emphysema and a left hemothorax following a chest injury. An exploratory thoracotomy revealed a foreign body in the posterior thoracic wall in the angle between the subclavian artery and the arch of the aorta. Within forty-eight hours following removal of the foreign body the patient developed a large chylothorax; 1,000 cc. of chyle were removed each day for a week; then accumulation of fluid rapidly diminished.—*Traumatic Chylothorax Resulting from Battle Injury*, W. H. Berry, J. A. M. A., February 1, 1947, 133: 319.—(H. Abeles)

Pleural Calcifications.—The number of cases of pleural calcifications are such that they are no longer considered a rarity. X-ray films permit studies of their position, form, dimensions and even their structure. Particularly important in their etiology is thoracic trauma associated with hemothorax. Other causes may be sero-fibrinous pleurisy, therapeutic pneumothorax and purulent pleurisy. Few symptoms may suggest pleural changes: bronchitis, emphysema or chest pain, usually vague, which enables one to discover pleural calcifications during the course of roentgen examination. Frequently these symptoms are unrelated to the presence of the calcifications. The silence of these lesions contrasts notably with the severe pain caused by the needle, during an exploratory puncture, coming in contact with an area of such hardness as to suggest contact with a rib rather than an intercostal space. Two films are of value in the study of these lesions: one to demonstrate the broad surface of the calcification, the other to

show its outline in profile. Diagnosis of such shadows is usually easy because their density exceeds that of parenchymal markings. They are rarely homogeneous, usually only their borders are clear-cut and very opaque, the central areas appearing areolar or fenestrated with linear opacities delimiting round or oval areas. Two sites of predilection for pleural calcifications are: the costovertebral gutter and the axillary region; less frequently, the anterior chest or diaphragmatic areas. Tomographic studies permit topographical localization; discovery of perhaps more than a single lesion when several shadows are superimposed on a standard film. Pleural calcifications also may mask a subjacent pulmonary lesion, which would be missed without body-section serial films. A case history is given in which honeycombing in the right lung was hidden by a pleural calcification in the standard film; tomograms demonstrated the otherwise invisible intrapulmonary lesions. Another case history is given to illustrate how the area of central rarefaction in a pleural calcification may be mistaken for an intrapulmonary cavity without recourse to laminagraphic studies in doubtful cases.—*De l'intérêt de la tomographie dans les calcifications pleurales*, J. Olmer, F. Santamaria & M. Lallemand, *Presse méd.*, December 25, 1946, No. 63, 852.—(P. Q. Edwards)

Intrapulmonary Air Pressure.—This paper endeavors to present the importance of having an intimate knowledge of the dynamics of the pulmonary circulation, of the anatomy and physiology of the air sacs and the circulation within the pulmonary capillaries.—*Intrapulmonary Air Pressure and Its Relation to Pulmonary Capillary Flow*, W. W. Wasson, *Am. J. Roentgenol.*, May, 1946, 55: 575.—(J. E. Farber)

Erythema Nodosum.—In tuberculosis, erythema nodosum generally appears when the pre-allergic phase passes into the allergic phase; erythema nodosum and tuberculin conversion are considered to be parallel phe-

nomena. In some cases, the former occurs in later stages of tuberculosis, and the combination of erythema nodosum and negative tuberculin reaction is not uncommon. It occurs in some usually tuberculin-negative tuberculous manifestations and in cases in which the erythema is caused by organisms other than the tubercle bacillus, e.g. the streptococcus, or in rheumatic fever. Negative tuberculin reactions may be due to sarcoidosis. In this disease which many investigators regard as a special form of tuberculosis, so-called positive anergy exists. The fact that bacilli are usually not demonstrable in the tissues, combined with tuberculoid structures without caseation, is evidence of hyperergy. Thus it is not surprising that erythema nodosum can appear as an allergic skin reaction in sarcoidosis. In 1945, 10 tuberculin-negative patients with erythema nodosum were observed. Lemming found that in sarcoidosis the tuberculin reaction remains negative even after BCG vaccination. This is evidence for the tuberculous etiology of the disease. Skin lesions appearing at the site of the vaccination and enlarged regional lymph nodes present the histological picture of sarcoidosis. Biopsies of such post-vaccination lesions have in a number of cases lent strong support to the diagnosis. In 5 of the 11 cases reported this procedure favored the diagnosis of sarcoidosis. This diagnosis is considered to be well established in cases with bilateral hilar adenitis, negative tuberculin reaction after BCG vaccination and with the histological picture of sarcoidosis in the post-vaccination lesions.—*Tuberculin-Negative Cases of Erythema Nodosum or Erythema Exudativum Multiforme*, O. Forsman, *Acta med. Scandinav.*, 1946, 126: 393.—(O. Pinner)

Amyloidosis of Lungs.—A proved case of primary amyloidosis is presented, involving mainly the lungs, mediastinum, lymph nodes and spleen. Roentgenographic characteristics include enlarged bilateral hilar densities and a linear and finally nodular peritruncal infiltration widely disseminated in the paren-

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chyma of the lungs. In the light of autopsy findings these roentgenographic changes are due to the deposition of fibrous tissue and amyloid material in the lungs, hila and mediastinum.—*Primary Amyloidosis of the Lungs*, P. R. Dirkse, *Am. J. Roentgenol.*, November, 1946, 56: 577.—(J. E. Farber)

Pulmonary Infarcts.—At the Massachusetts General Hospital pulmonary infarction has been one of the two most common post-operative complications. Early recognition of infarcts is of extreme importance since the condition may be the first sign of massive fatal embolism and since certain preventive measures against the condition are now available. Proper technique of roentgen examination to demonstrate the infarct includes fluoroscopy, spot films and X-ray films in both posteroanterior and lateral projection. The size of an infarct varies from a small thin lesion to a large almost lobar area. The shape is dependent on its location but it is always peripheral with its long dimension lying parallel to the pleura. An infarct is at first indistinct, later more sharply circumscribed assuming a linear shape, finally a very thin linear scar. Approximately 75 per cent of infarcts occur in the lower lobes.—*The Technique of the Roentgenologic Demonstration of Pulmonary Infarcts*, L. L. Robbins, *Am. J. Roentgenol.*, December, 1946, 56: 736.—(J. E. Farber)

Lobectomy.—A total of 196 consecutive operations are reported with one death (the fourth case) (the number has since been increased to 236 without further mortality). All patients except 4 were under 40 years, and most were under 30. Lobectomy was performed in bronchiectasis, pulmonary cyst, chronic suppurative, bronchial adenoma, adenomatosis, tuberculosis, neurogenic sarcoma and actinomycosis. Bilateral lobectomy for bronchiectasis was performed in 4 patients. A fifth that had previously had right lower and middle lobes removed, had lingula and left lower removed. Preoperative penicillin was used by all routes plus postural

drainage and bronchoscopic aspirations in indicated cases. Intratracheal anesthesia was used in all cases. Individual ligation was used after the first 2 cases. All patients were bronchoscope immediately after surgery. Closed drainage with a water-trap was used on all cases and usually discontinued after two days. Intranasal oxygen was routine, but discontinued usually after twelve hours. Maintenance of a clear airway was the most imperative postoperative feature done by means of intratracheal, transnasal suction till patient could cough actively. Early movement was insisted upon. Patients were fully ambulatory by the end of a week. Phrenic paralysis was induced in the majority of patients after full aeration of the remaining lung, to diminish pull on bronchial stumps with unsatisfactory pleural covering, and to aid in relief of deep seated pain and tightness in the chest. Complications occurred in 27 cases. Empyema accounted for 15. Jaundice of undetermined origin occurred in 7. Pneumothorax several weeks after operation occurred in 2. Atelectasis requiring bronchoscopy developed in one, and cerebral embolism followed by recovery was encountered in one. One patient died twenty hours after right lower lobe lobectomy for bronchiectasis, from cerebral and pulmonary edema.—*A Report of One Hundred Ninety-six Lobectomies Performed at Kennedy General Hospital Chest Surgical Center from 1943 to 1946, with One Death*, R. H. Mcade, Jr., E. B. Kay & F. A. Hughes, *J. Thoracic Surg.*, February, 1947, 16: 16.—(J. H. Cope)

Pneumonectomy in Childhood.—This is a follow-up on 3 previously reported cases which were first studied during growth period. These patients have now attained their complete growth and one case is added to the report. The technique of catheterization of the right heart has been added to the study for a better evaluation of the state of the lesser circulation and the cardiopulmonary functions. The method used consisted in the study of the pulmonary volumina, the ventilatory efficiency, the efficiency of alveolar

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pneumothorax can be safely carried out using measured positive pressure at the termination of the operation. Uninvolved lung tissue should be reexpanded frequently during the course of the operation in an attempt to minimize the dangers of postoperative atelectasis and to assist the surgeon in locating lines of demarcation. Whole blood transfusion during surgery will usually prevent shock. Immediate postoperative bronchoscopy with aspiration and X-ray examination before patient leaves the table will reduce pulmonary complications. Fluids intravenously in pulmonary resection should be given sparingly, especially during surgery and in the immediate postoperative period, for pulmonary edema may result. Many different types of anesthetic agents have been used in thoracic surgery during, and since, World War I. With the advent of carbon dioxide adsorption and endotracheal anesthesia thoracic surgery has become much safer. The large series of thoracotomies performed, including 559 lobectomies and 109 mediastinal tumors under ether-oxygen maintenance anesthesia indicates the safe character of this anesthetic agent.—*Anesthesia for Thoracic Surgery in the United States Army*, L. H. Mouscl, *J. Thoracic Surg.*, February, 1947, 16: 91.—(J. H. Cope)

Surgery in Myasthenia Gravis.—In 32 cases of *myasthenia gravis*, thymus tumors were found in 15, and no tumor in 17, that is in those cases that were operated. It is concluded that thymectomy was of enough value in the treatment of *myasthenia gravis* to warrant surgery in all cases with severe or progressive disease and when the patient's condition permits. The sternum-splitting incision was used. Preoperative preparation with neostigmine is essential, with attention to nutrition, and hospital rest with preoperative penicillin. Neostigmine, penicillin and oxygen should be given as routine postoperative medication. Intratracheal suction and a respirator must be immediately available. The postoperative course is unpredictable but patients are usually ready for discharge in ten to fourteen days.—*Surgical Treatment of*

Myasthenia Gravis, O. T. Cloggett & L. M. Eaton, *J. Thoracic Surg.*, February, 1947, 16: 62.—(J. H. Cope)

Curare in Anesthesia.—This technique requires preoperative medication of a short acting barbiturate, morphine and scopolamine. Nitrous oxide and oxygen were started on operating table. When anesthesia and adequate air were assured, 200 mm. of curare were given intravenously. Controlled respiration was used for about five minutes till maximum relaxation was attained. An endotracheal tube was then inserted. The same concentration of nitrous oxide and oxygen required for good oxygenation before curare must be continued, as the usual signs of anesthesia are completely masked. Curare was used in children in calculated dosage with good effect. Additional curare is given during anesthesia to produce apnea as desired. Patients were awake and able to answer questions before leaving the operating table. Muscular weakness persists for several hours and careful after-treatment is necessary. The advantages are that there is no explosive mixture used, so the electrocautery is safe. The patients remain in excellent condition through many hours of surgery and still are awake by the time they reach the ward. The average date of ambulation and discharge indicates how little the anesthesia upset the patients, the days being the second and fourteenth, respectively. Eight deaths occurred, of which 2 may have been due to some influence of the anesthetic.—*The Use of Curare in Anesthesia for Thoracic Surgery*, H. B. Stephens, P. Harsoun & F. E. Beckert, *J. Thoracic Surg.*, February, 1947, 16: 50.—(J. H. Cope)

Epidemic Myalgia.—Bornholm disease, often seen in benign and variable epidemic form throughout many countries, is also known as contagious epidemic muscular rheumatism, epidemic pleurisy, epidemic myalgia, pleurodynia, Devil's grip or *Sommerfieber*. Sylvert, in Denmark, who has observed almost 100 cases during two epidem-

ics, one in the Baltic island of Bornholm, the other in Copenhagen, characterizes the disease as follows: It occurs only between May and September, with children and young adults being largely affected. The onset is usually abrupt with aching pains. These pains are usually localized in the pectoral or upper abdominal muscles, less frequently in the shoulder or lumbar muscles. The affected muscles become indurated or nodular with hypersensitivity to touch and contraction. General symptoms, such as fever, sweating and headache, are usually moderate; myalgia and fever may persist for two or three days, but often, after a twenty-four-hour respite, symptoms may recur with the myalgia in a different group of muscles. The disease is almost always benign and results in complete cure. Possible complications include dry or serous pleurisy, pericarditis, otitis media, bronchitis, pneumonia, orchitis or even encephalitis. Epidemic characteristics of the disease are clear, spreading by direct contact. The incubation period varies from two to four days; etiology is unknown. Diagnosis is based upon recognition of the epidemic character of the disease; even the pleuropneumonic aspect of the disease, when associated with the characteristic myalgias in the presence of an epidemic, should be recognized as part of the same process. Abrupt onset of muscular pain, without antecedent history of other disturbances, should make one think of Bornholm disease; children are often stricken suddenly by pain in the midst of play. Blood studies offer no diagnostic aid. Differential diagnosis includes rheumatic myositis, in which joints are involved, poliomyelitis with its spinal fluid changes, meningitis may be confused when the myalgias are in the neck, but diagnostic changes in the spinal fluid and clinical picture are evident; benign serous meningitis may be similarly differentiated. Treatment of the disease is symptomatic. — *Forme pleuropulmonaire et pseudopéritonéale de la myalgie épidémique, R. Bogaert, Presse méd., December 28, 1946, No. 64, 881.*—(P. Q. Edwards)

Antihistamine Substances.—The effect on vital capacity of standard intravenous doses of histamine was quantitatively established in selected asthmatic subjects. It was found that, although in a given subject there could be variation in response to the same dose of histamine from time to time, depending on the severity of the asthmatic state, at any given time closely similar quantitative responses to consecutive doses of the same amount of the drug could be elicited. The response consisted of temporary decrease in vital capacity, attributed to bronchoconstriction. The special features of the response were time of onset, maximum decrease reached and duration of effect. Following this, antihistamine drugs were administered and the effect on subsequent intravenous doses of histamine noted. In a typical experiment, the maximum decrease in vital capacity caused by histamine was 1789 cc. Following 10 mg. benadryl intravenously, the response to the same dose of histamine as previously used was 721 cc. After 30 mg. benadryl intravenously, the return to the control response to histamine was delayed over three and one-half hours. Pyrabenzamine hydrochloride, in 3 subjects, gave no consistent protection against histamine. Theophylline with ethylenediamine intravenously administered gave marked protection. Epinephrin in doses as low as 0.1 cc. of a 1:1000 solution gave marked protection which lasted one hour. Ephedrine intramuscularly gave satisfactory protection, delayed in onset but prolonged in duration. In one subject atropine gave moderate protection against histamine.—*The Action of Histamine on the Respiratory Tract in Normal and Asthmatic Subjects, J. J. Curry, J. Clin. Investigation, November, 1946, 25: 785; and The Effect of Anti-Histamine Substances and Other Drugs on Histamine Bronchoconstriction in Asthmatic Subjects, J. J. Curry, J. Clin. Investigation, November, 1946, 25: 789.*—(A. A. Cohen)

Transmission of Leprosy.—The exact manner of transmission of leprosy is still unknown. Sixty per cent of the author's native patients

(Southern Rhodesia) and some 16 European patients had never been in contact with the disease. Close and intimate contact does not explain transmission of the disease. Suspicion fell on the cockroach as a vector. In 23 per cent of cockroaches caught in the huts of patients *Mycobacterium leprae* was found. In skin wounds and scars caused by the bite of cockroaches *M. leprae* was frequently found. The numerous bacilli found in roaches which have ingested them suggests that multiplication in the roach has occurred. The bacilli remain unchanged and presumably alive in the dry droppings of the roach, for at least sixteen months. In 5 cases roaches ingested *M. leprae* from the dried feces of other roaches fed on positive material; "this may be found to continue indefinitely, so that the real source of infection of Hansen's disease may prove to be the droppings of cockroaches." Strongly acid-fast "Oval Bodies" were found in 70 per cent of all roaches examined, and only occasionally in routine examinations of blood and smears from man. Reenstierna, director of the Department of Hygiene and Bacteriology at the University of Upsala, Sweden, recognized them as greatly resembling, and probably identical with, the "Maternal Fungus" he discovered in 1912 in a blood culture from a leper and later on found in several other patients. The leprosy bacillus may be passed to man either by the bite of the roach or by the dried droppings of the roach rubbed into the skin. Infection from man to man is unlikely.—*Transmission of Hansen's Disease (Leprosy)*, B. Moiser, *Acta med. Scandinav.*, 1946, 126: 347.—(O. Pinner)

Johne's Bacillus Antigen.—The author has demonstrated in previous publications (*J. Immunol.*, 1945, 51, 279 and 53, 127) an antigen in the intestinal mucosa of sheep infected with *M. paratuberculosis*. The antigen is "masked" in fresh mucosa and will not react with sera from infected sheep in the complement fixation test. When the tissue is dried and thoroughly ground before extraction, the antigenic substance, which appears

to be protein, becomes available in serologically active form. This substance is shown to be insoluble within the pH range of 3.0 to 5.0. Preliminary acidification of dried ground mucosa to this region and subsequent extraction of the sedimented material with saline at pH 9.0 and at 100°C. results in more active extracts than were previously obtainable. It is suggested that there may be two "masking" mechanisms; one is destroyed by mechanical grinding of the dried tissue, the other is removed by treatment with acid.—*A Specific Antigen Recovered from Tissue Infected with M. Paratuberculosis (Johne's Bacillus): III. Further Studies on the Nature of the Antigen and on Methods for Demasking It*, B. Sigurdsson, *J. Immunol.*, February, 1947, 55: 131.—(S. Raffel)

Streptomycin in Veterinary Medicine.—The use of streptomycin in veterinary medicine has been based principally on the use in humans. No definite animal dosage is as yet known. Anatomical and physiological differences among mammals will undoubtedly result in various responses to this drug. Control of infectious diseases in domestic animals should be based primarily on prevention, which requires the application of hygienic principles first and immunological procedures second. It is unlikely that streptomycin will be available to the veterinary profession for some time. Streptomycin in veterinary practice is limited by the requirement of frequent dosage. This can be overcome in hospitalized dogs and cats, but for farm animals it is obviously not economically feasible. This may be overcome in part by the use of vehicles to delay absorption. Certain organisms acquire resistance to streptomycin. The question arises then, will resistant, virulent microorganisms be transmitted from treated animals to susceptible animals and produce disease that will not respond to streptomycin therapy? It is obvious that one would not use streptomycin to treat bovine tuberculosis, anthrax, glanders or rabies. Valuable animals afflicted with brucellosis may prove to be worthy patients.

Pyelonephritis in cattle may be amenable to this therapy. Actinomycosis and mastitis may also be added to this group.—*Streptomycin in Experimental Infections and Its Possible Use in Veterinary Therapeutics*, A. G. Karlson & W. H. Feldman, *J. Am. Vet. M. A.*, February, 1947, 110: 63.—(R. W. Clarke)

Tuberculosis Campaign in Brazil.—On June 21, 1946, President Dutra of Brazil signed a decree providing for an intensive national campaign against tuberculosis under the direction and control of the National Department of Public Health. While the entire nation is to be covered, special attention will be centered on the areas with the highest tuberculosis incidence. In support of the decree the Minister of Education and Health stated that tuberculosis was the communicable disease with the highest death rate in Brazil, the number of yearly deaths being estimated at 80,000 and the number of patients being placed at 800,000. The situation is getting worse, and epidemic outbreaks are actually occurring, especially in the most thickly populated centres. Death rates vary from 300 to 500 per 100,000 inhabitants, the highest (above 400 per 100,000) in the cities of Vitoria, Salvador, Porto Alegre and Belem, with Rio and Niteroi coming next. The efforts so far made have been inadequate and incoordinated and the results spotty. Success depends on efficient organization, uniformity of action and constant expert supervision by the National Tuberculosis Service of the National Department of Public Health. More active support should also be obtained from members of national tuberculosis organizations now numbering nearly 3,000,000. In commenting on these developments, the Editor of *Clinica Tisiologica* adds that, with the exception of Sao Paulo, which from the beginning of the century has stabilized its tuberculosis death rate around 100 per 100,000 and Terezina, Curitiba and Cuiabá with rates which have risen lately from 50 to 200 per 100,000, the rates in the other 17 State capitals run from 250 to 500 per 100,000.

Most of the large Brazilian cities are now going through the phase of massive tubercularization. The relatively low figures at Sao Paulo are most likely due to its predominantly European population, as is also the case with Buenos Aires and Rosario in Argentina and Montevideo in Uruguay. The problem is far different and much worse in the other South American cities. Should urban rates apply to the whole of Brazil, the annual number of tuberculosis deaths would be 118,350 for a 45 million population. The number of beds available for patients in the whole country does not exceed 12,410, most of which are provided by the Federal Government. Prompt provision of hospital beds and dispensary facilities, extension of mass surveys, intensive use of BCG in the newborn, creation of tuberculosis professorships in medical schools and intensive study of the epidemiology of the disease in Brazil are recommended.—*Campanha Nacional contra a Tuberculose*, R. Fernandes, *Clin. Tisiol.*, April-June, 1946, 1: 1, and 146.—(A. A. Moll)

Tuberculosis in St. Lawrence Basin.—In three years, 31,265 persons, about 22 per cent of the population of the St. Lawrence basin, were fluorographed by a traveling mission from the St. George Sanatorium. Of this group, 702, or 2.2 per cent, were diagnosed tuberculous, 316, or 0.9 per cent, were considered suspicious and 1,556, or 5 per cent, had primary infections. Of the diagnosed cases, 48 per cent were minimal, 31 per cent were moderate and 21 per cent far advanced.—*Trois années de dépistage de la tuberculose dans le bas St. Laurent par les médecins du Sanatour St. Georges*, J. A. Couillard, *Laval méd.*, December, 1946, 11: 1033.—(E. Bogen)

Tuberculosis in Moravia.—The mortality of tuberculosis in Moravia was lower (191 men and 179 women per 100,000 inhabitants) than in other parts of Czechoslovakia before World War II. During the war the morbidity and the mortality increased and this

increase is persisting at present. Compared with other European countries, only France, Hungary, Rumania and Bulgaria reported higher mortality of tuberculosis.—*Tuberculosis Mortality in Moravia (Umrtnost tuberkulosou v zemi Moravskoslezské)*, P. Pur, *Praktický Lekar*, (Czech), September, 1946, 14: 390.—(O. Felsenfeld)

had little means of transportation. In order to limit the spread of tuberculosis among nursing personnel, extra courses were given to instruct them in the prevention of tuberculosis. Other preventative work was quite limited and in only a few cities was it possible to fluoroscope the school-children. BCG vaccine was not used.—*From the Report of the Chief Public Health Officer for the year 1948*, Dr. C. Banning, *Verslagen en mededeelingen betreffende volksgezondheid*, September, 1946.—(K. Van Leeuwen)

Tuberculosis Administration in America.—

Two leading Australian tuberculosis specialists visited more than 40 American tuberculosis sanatoria and clinics and report on their four months observations, in 66 pages. Mass radiography is commended but the need for protection of operating personnel, and for provision for the follow-up and care of new cases discovered is stressed. One sanatorium bed for each 5 cases discovered in the community, or about 1 bed per 1,000 population is advised rather than the old standard based on the number of deaths per year. About 400 beds was considered the optimum size of a sanatorium. Sanatorium construction is discussed and the advantage of placing the kitchen on the top floor noted. Rooms with no more than 6 beds are advised instead of large wards. A chest clinic is needed for every 300,000 population, with adequate visiting nurses and other staff. It is recommended that the Governments concerned pay an amount equal to the basic wage to breadwinners suffering from tuberculosis and unfit for work. The qualifications and salaries of staff members and other help, and the use of patient and ex-patient help on the staff are reviewed. The indications for artificial pneumothorax, thoracoplasty, and especially for pulmonary resection are discussed and the treatment of empyema outlined.—*Reports on Tour of Canada and United States of America*, H. M. James & C. J. Officer Brown, Government Printer, Melbourne, 1946.—(E. Bogen)

Tuberculosis in Holland.—The incidence of tuberculosis has increased. The scarcity of food, especially fats, the necessity to live in crowded quarters due to voluntary and forced evacuation, the shortage of medical personnel in hospitals and sanatoria, the closer contact of people in overcrowded trains and other means of transportation, the long distribution lines in central kitchens and distribution offices, were all favorable to the spread of tuberculosis. Besides physical factors, psychological factors played a great rôle and diminished the resistance of the population to tuberculosis. The mortality from pulmonary tuberculosis increased 87.5 per cent from 1939 to 1943. During World War I there had been an increase of 44.8 percent from 1914 to 1918. The total number of people who consulted the tuberculosis clinics increased from 60,000 in 1939 to 157,000 in 1943. Of these, 8,840 cases turned out to have active tuberculosis in 1939 and 18,571 in 1943. This represents an increase of 110 per cent. In Amsterdam the increase of new active cases was 154 per cent. Only 46 per cent of the patients who died of tuberculosis were ever seen in a clinic. During the war an increasingly large number of people started to make use of the clinics because of the rising fear of tuberculosis and the material gains incurred. Tuberculous patients were not sent to Germany and received extra rations of food. Great difficulties were encountered in the care of patients. Many sanatoria had to be evacuated, there was a great shortage of linen, soap, disinfectants. People often preferred to keep their children at home because of the many uncertainties and the difficulties in traveling. The nurses had to cover large districts and

Tuberculosis in Mentally Ill.—A total of 2,000 patients were examined at the mental hospital in Cery for the presence of pulmonary tuberculosis. Chronic fibro-calcified forms of the disease were found in 28 per cent, open tuberculosis in 1 to 2 per cent. Schizophrenics and patients with senile dementia were most frequently affected. Two hundred and nine autopsies carried out on this group revealed advanced tuberculosis in 57 per cent of the cases.—*Une enquête phthisiologique a l'Asile de Cery, R. Burnand & G. Schneider, Bull. d. Schweiz. Akad. d. Med. Wissensch., 1946, 2: 77.*—(B. Gerstl)

Bronchiectasis and Primary Tuberculosis.—Pulmonary tuberculosis is frequently a cause of bronchiectasis observed in childhood. In a careful follow-up study of 37 children with primary tuberculosis Willis *et al.* found manifest bronchial dilatation in 24 of these children. It was demonstrated that in every instance the segment of the lobe with bronchiectasis was the previous site of the tuberculous process. The conclusion reached was that pulmonary tuberculosis in children is frequently complicated by tuberculosis of a bronchus and that these bronchial lesions are often associated with obstructive pneumonitis. Further, a large number of these obstructive lesions associated with tuberculosis of a bronchus revealed bronchiectasis in the segment or lobe involved in the obstruction. The dilation of the bronchus usually extended from the root of the lung to the periphery.—*Bronchiectasis following Primary Tuberculosis, Editorial, Am. J. Roentgenol., January, 1947, 57: 116.*—(J. E. Farber)

Primary Tuberculosis in Adults.—X-ray signs of old pulmonary processes were found in all cases (27.5 per cent) found negative in a tuberculin survey made in 1939 among 771 inmates of two Rio homes for old men. Saenz' experiments suggest that disappearance of allergy in old people is due to lack of stimulation by superinfections. Anatomical and clinical evidence also supports this conception.

Surveys made in young physicians, medical students and nurses exposed to direct hospital infection show that the disease attacks allergic as well as anergic individuals. At the Almeida Magalhães and Miguel Pereira Hospitals at Rio, old staff members with more than six years of professional contact with the disease, usually showed a low allergy. Those recently employed, while also showing a low allergy when tuberculin-tested, became more highly allergic under contact with tuberculous patients. It was in the latter group that cases developed. This led to the transfer to other work of new staff members who became tuberculin-positive with strong phlyctenular reactions if the latest roentgenogram, as compared to the one taken on entrance, showed activation. A clinical and X-ray study of 314 necropsies in the two hospitals justified the division of all apparently primary cases into three groups: 1.) genuine primary infection, Borrel type, 2.) primary infection type, and 3.) secondary-primary complex. In the first type, described by Borrel in Senegal soldiers during World War I, caseated parenchymatous lesions coincided with enlarged, swollen nodes, also caseated. These cases totaled 72 (22.9 per cent of the series). In the second group, the primary process was complicated by the coexistence of fibrotic or fibro-calcific lesions, bearing witness to previous infections, entirely or partially overcome. There were 138 cases (23.9 per cent) of this type. The third group included only one case in a 30-year-old woman and was characterized by a completely calcified hard process in the lung with large caseous mesenteric nodes, typical of a virgin soil. These observations lead to the conclusion that the one essential in the prevention of primary tuberculosis is the use of BCG in all healthy anergic persons of all ages. Vaccinated persons who may contract tuberculosis will thus develop a reinfection type with a more favorable response to collapse therapy.—*Clinica da tuberculose primaria do adulto, R. Fernandes, Clin. Tisiol., April-June, 1946, 1: 5.*—(A. A. Moll)

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Primary Tuberculosis in Adults.—Two elements are generally accepted in the diagnosis of primary infection: tuberculin conversion and lymph node tuberculosis. Enlargement and caseation of the hilar nodes is the usual response of the infantile organism to the attack of the Koch bacillus. Adults who have this form of tuberculosis are often of the infantile type and some show retarded genital development. Endocrine imbalance has a definite influence on the development of the histological structure of the lung. But glandular tuberculosis has also been observed in adults who have had definite histories of previous tuberculous infection. Here, complete healing of the previous disease with disappearance of the allergy has taken place. Consequently, a person who does not react to tuberculin may either be normergic or may have overcome completely cutaneous sensitivity to tuberculin. In Montevideo, systematic autopsies of all 20-year-old persons killed in accidents showed that calcifications were present in 100 per cent, although only 80 per cent of that group are tuberculin reactors. The calcifications were always small and generally found in the lower pulmonary fields. In some cases, discrete abortive lesions were present in the nodes. Only when the infection is repeated by new exposures to contact, is tuberculin allergy maintained. Otherwise, the foci become sterile. The statistics prove that after fifty years the index of allergization decreases in the population, although small calcified foci are always present. Tuberculin-negative adults must be considered as having completely recovered from the disease and many will respond to a new tuberculous infection with a primary lesion as seen in children. This is especially true for certain races (Negroes, Indians, Mulattos etc.). If transplanted from their normal living conditions into the big cities, the change in nutrition and activity, unaccustomed industrial work, the difficulties of maintaining adequate living conditions, alcoholism etc., will cause a profound disturbance of the defense mechanism and give rise to the appearance of acute exudative and caseous forms of tuberculosis with frequent glandular participation. Persons of all races, deprived of their usual living conditions as in the last years in Europe, may respond to the infection with a childhood type of disease, whether their reaction to tuberculin is positive or negative. In the white race, these patients were always found to have underdeveloped secondary sexual characteristics. There is not only a hereditary transmission of the disposition to acquire tuberculosis but also a special disposition to variations of the disease with typical topographic and pathological features and similar prognosis. The latter is responsible for the variations of infectivity in certain families or of a family will survive a certain type of the disease whereas another member dies from it. The conclusion is that primary tuberculosis of the adult is due to constitutional particularities and not to biological ones. The clinical examination of these patients should always be combined with biometric, genetic, and social studies.—*La tuberculosis primaria y de reinfección del adulto; su significado clínico, epidemiológico y social*, F. D. Gomez, *Hoja fisiol.*, December, 1946, 6: 420.—(W. Swienty)

Phlebitis in Tuberculosis.—Phlebitis often develops late in the course of pulmonary tuberculosis, but is rare before the tuberculosis has progressed. Two instances are described in which acute phlebitis remained unilateral and did not adversely influence early pulmonary tuberculosis.—*Phlébite précoce chez deux tuberculeux*, R. Desmoules, *Laval méd.*, February, 1947, 12: 113.—(E. Bogen)

Mediastinal Displacement by Caseous Lung.—Mediastinal shift from ordinary causes is towards the involved side. Pulsion (or contralateral) displacement may be caused by unilateral cystic, neoplastic or emphysematous pulmonary processes. A child, age 8 months, is reported. He was studied for a week before death and autopsy was performed. The

physical and X-ray signs were those of a massive left pleural effusion with mediastinal shift to the opposite side. Aspiration produced thick tuberculous pus. Autopsy showed obliteration of the left pleural space by adhesions; and enlarged left lung, weighing nine times as much as normal; and an almost complete replacement of the lung substance by caseation.—*Displacement of the Mediastinum Due to Pulsion by a Caseous Tuberculous Lung without Pleural Effusion*, J. F. Miller & B. H. Kean, *J. Pediat.*, February, 1946, 28: 200.—(W. H. Oatway, Jr.)

Undetected Tuberculosis.—Two hundred consecutive autopsies were done in a general hospital which does not knowingly admit tuberculous patients; 41 cases of tuberculosis of all types were found. Two age groups were distinguished: below and above 20. In the first group were 24 autopsies, 3 of which revealed generalized tuberculosis. Of 176 autopsies done on persons above 20, 38 cases of tuberculosis were found. Of all 41 cases, 31 died of causes other than tuberculosis, and the patient as well as the physician were completely unaware of the disease. In 18 of these 31 autopsies, extensive caseo-caverno-pneumonic or miliary disease was found. The other 13 cases showed residual tuberculosis in 5, productive glandular disease in 5, fibrotic in 2 and pleural tuberculosis in one. Of the remaining 10 cases, 8 patients ignored the disease but their physicians had established the diagnosis. In view of the high incidence of undetected tuberculosis, the conclusion is that no patient should be admitted to a general hospital without X-ray examination of the chest.—*Anatomia patologica de la tuberculosis inaparente*, A. de Paula, *Prensa méd. argent.*, November 15, 1946, 33: 2300.—(W. Swienty)

Treatment of Tuberculosis.—Disposition for tuberculosis exists only in individuals with alkalotic constitution. The alkalotic constitution is a good medium for the tubercle bacillus. The determination of the pH in the blood helps in differential diagnosis: values toward the acid side speak against

tuberculosis. Shifting of the pH toward the acid side in tuberculous patients is an objective sign of healing. Shifting of the acid-base balance toward the acid side and maintenance of acidity is possible. It is done by inhalation of CO₂, once or twice daily for five minutes, and by oral administration of ammonium chloride. At the same time the blood-calcium should be increased, which can be done with the help of large doses of human serum. The change of the medium has a bacteriostatic effect and the calcium salts, which are deposited near the bacteria, have a bactericidal effect. Patients with alkalotic constitution are unsuitable for employment in a tuberculosis institution because of danger of infection. It is advised to do blood pH and calcium determinations in employees of tuberculosis institutions at regular intervals.—*Neue Wege der Tuberkulosebehandlung*, V. Sajgó, *Wien. klin. Wchnschr.*, September 18, 1946, 58: 529.—(G. C. Leiner)

Diasone in Pulmonary Tuberculosis.—Diasone in the treatment of 38 patients with pulmonary tuberculosis in the Huipuleo Sanatorium in Mexico proved disappointing. Out of 29 cases with cavitation, the result may be called good only in 3 early cases with few and small cavities. In only 2 of these did sputum become negative. In 6 cases cavitation progressed. The average daily dose was 0.9 g. for persons weighing 110 lbs. or more and 0.6 g. for those under that weight. Dosage had apparently little influence on the result, as cavities healed with blood concentrations from 0.5 to 4 mg. In view of the frank toxicity of the drug, use of a supplementary antitoxic medication might improve the outcome. Tuberculous enteritis was favorably affected in 3 cases, and an ulcer of the soft palate healed under treatment. A trial of the drug in extrapulmonary tuberculosis might be worth while.—*Quimioterapia de la tuberculosis (resultado de ensayos con diasone)*, D. G. Alarcón & E. García Salazar, *Clin. Tisiol.*, July-September, 1946, 1: 159-184.—(A. A. Moll)

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Streptomycin and Tubercle Bacilli.—On the basis of extensive *in vitro* and *in vivo* experiments, it is concluded that streptomycin is capable of retarding the growth of human tubercle bacilli. The high concentration of streptomycin required in a good nutrient medium indicates that adequate concentration *in vivo* can only be attained for brief periods. Lung, liver, spleen and kidneys of guinea pigs that had received large doses of streptomycin one hour or one day before death did not retard growth of tubercle bacilli in broth. This is taken as evidence that streptomycin does not enter these organs in appreciable amounts for any significant time. Streptomycin is, therefore, considered as an encouraging milestone in the chemotherapy of tuberculosis, but its application is of limited value.—*The Tubercle Bacillus and Fundamental Chemotherapeutic and Antibiotic Action*, H. J. Corper & M. L. Cohen, *Yale J. Biol. & Med.*, 1946, 19: 1.—(B. Gerstl)

Experimental Streptomycin Poisoning.—Administration of various doses of streptomycin to 42 monkeys, 11 dogs, 350 rats, 100 mice, 10 chickens and 154 guinea pigs produced a variety of lesions, especially temporary fatty changes in the liver and less often in the kidneys. Disturbances in equilibrium was noted but the responsible lesion was not found.—*Pathologic Changes Resulting from the Administration of Streptomycin*, C. W. Mushell & H. S. Marland, *Arch. Path., December, 1946*, 42: 619.—(E. Bogen)

Streptomycin in Oil and Beeswax.—Since the indications for slow absorption with prolonged therapeutically effective serum levels are the same as in penicillin therapy, the purpose of this investigation was to study the absorption and excretion of streptomycin suspended in peanut oil and beeswax and in solvecillin (a commercial lanolin-like substance) administered by intramuscular injection. Local reactions were quite mild and similar to those produced by similar amounts of streptomycin dissolved in sterile saline

solution. It was found that streptomycin suspended in peanut oil and beeswax is not absorbed from the muscles as readily as penicillin. This slow absorption probably results in greater fixation or inactivation of streptomycin in the tissues, accounting for the low serum levels and reduced urinary excretions. Maintenance of minimum effective serum levels over a period of six hours requires the injection of more than 500,000 units per dose. Absorption after intramuscular injections of the compound emulsified in solvecillin is more pronounced and similar to that following injections of the compound dissolved in saline solution, but serum levels following intramuscular injections of 250,000 units in solvecillin are not as high as those following intramuscular injections of 500,000 units suspended in peanut oil and beeswax.—*Administration of Streptomycin in Peanut Oil and Beeswax and in Solvecillin*, L. A. Kolmer, A. Bondi, H. F. Warner & C. Dietz, *Science*, October 4, 1946, 104: 315.—(E. A. Rouff)

Streptomycin in Childhood Tuberculosis.—Four children 7 months to 3 years of age with early pulmonary tuberculosis of the childhood type were treated with streptomycin. Each child received 20,000,000 to 30,000,000 units of streptomycin. Although the children showed extending disease prior to the institution of therapy none of them showed progression during streptomycin therapy. Defervescence, improvement in the general condition and regression of the pulmonary lesion were observed in all 4 cases.—*Streptomycin in Pulmonary Tuberculosis in Childhood: Results in Four Children*, H. N. Sanford & D. E. O'Brien, *J.A.M.A.*, March 8, 1947, 133: 691.—(H. Abeles)

Deaths during Artificial Pneumothorax.—Six cases are described. In 5 of them the pulmonary parenchyma was penetrated with the needle and a valvular pneumothorax resulted. The sixth patient died of heart embolism.—*Deadly Complications during Treatment with Pneumothorax* (Smrtici komplikace

pri leebe pneumothoraxem), O. Ruzicka, *Časop. lékař. česk.*, (Czech), December, 1946, 85: 1741.—(O. Felsenfeld)

Horner's Syndrome following Pneumolysis.—During the surgical severance of pleural adhesions an injury of the cervical sympathetic nerve was caused. Vasodilatation, lower tonus of the facial muscles and periodic sharp pain in the shoulder (Horner's complex) resulted.—*A Complication in the Autonomie Cervical Nerves Resulting from Thoracocautic (Komplikace na autonomním nervstvu krcním pri thorakokaustice)*, F. Novak, *Lekarske Listy*, (Czech), October, 1946, 1: 457.—(O. Felsenfeld)

Extrapleural Oleothorax.—In a 27-year-old man an extrapleural pneumothorax was instituted in November, 1939. The air was replaced with oil in April, 1940. In January, 1942, the oil was removed and in August, 1942, the extrapleural cavity was no longer visible. In a 26-year-old woman an extrapleural pneumothorax was instituted in January, 1940. The air was replaced with oil in April, 1940. The oil was removed in August, 1942, and in November, 1942 the extrapleural cavity was no longer visible. In the majority of the patients with oleothorax, the oil remains symptomless in the cavity and is, therefore, not removed. It is advisable to remove the oil after some time because complications may arise even after many years.—*Der Endausgang des extrapleuralen Oleothorax*, K. Domokos, *Wien. klin. Wchnschr.*, December 13, 1946, 58: 753.—(G. C. Leiner)

Pneumoperitoneum.—In 2 cases in which artificial pneumoperitoneum had been abandoned, extensive adhesions were found on attempted reinduction. In 3 other cases, no adhesions were found. It is suggested that, instead of complete abandonment, a shallow pneumoperitoneum be maintained if there is any possibility of future need of reinduction.—*Adhesion Formation after Pneumoperitoneum*, F. L. Corrigan, *Tubercle*, February, 1947, 28: 25.—(A. G. Cohen)

Avian Tubercle Bacilli.—Avian tubercle bacilli do not comprise a homogeneous serological group; rather, they belong to distinctly different serological types. To identify these types, complement fixation and agglutination reactions are both used. For the former, either alcoholic extracts, according to Schaefer's method, or bacillary suspensions heated to 80°C. for one hour are employed. The same suspensions serve for agglutination reactions, as all batches are smooth on Lowenstein's medium, producing a sufficiently stable suspension. Antisera are made by injecting rabbits intravenously two times per week for three or four weeks with 4 to 8 mg. of killed bacilli; the animals are bled six days after the last injection. At first these sera produce only a weak specificity and give complement fixation or agglutination reactions with all avian and even bovine bacilli. Treatment of the sera by absorption of antibodies for the heterologous strains produces a specific serum for homologous strains. Of 23 strains so tested, 12 belonged to type I and 10 to type II (Schaefer). A strain isolated from a tuberculous chicken did not resemble any of the known types: it produced an antiserum which, after absorption by a heterologous strain, showed specificity for the homologous strain. This serum, in non-absorbed state, reacts with all types of avian strains and with the guinea pig type III. But after absorption by heterologous strains, it has a specificity only for the homologous strain. This is apparently a new serological type of avian bacilli, distinct not only from types I and II but also from two other types described by Cabasso, Schaefer and Harpoth. Antiavian rabbit sera agglutinate greater dilutions than those which fix complement in the presence of bacillary suspensions; apart from this quantitative difference, results by the two methods are essentially comparable. An antigen common to all types of avian bacilli exists which is not present in tubercle bacilli of mammals. This common antigen is not strictly specific for avian bacilli, as it occurs also in saprophytic bacilli of guinea pigs (guinea pig type

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III). This type absorbs all antibodies in antiavian sera, except the specific antibodies of the type; conversely, the antiserum prepared from this type reacts with all avian types, even after absorption by bovine or human bacilli. The dominant and truly characteristic antigen of avian bacilli is therefore the type specific antigen and it is necessary to prepare specific sera for each type to identify the avian strains by serological methods.—*Contribution à la classification sérologique des bacilles de la tuberculose aviaire*, F. Rolach, *Ann. Inst. Pasteur*, January, 1947, 73: 71.—(P. Q. Edwards)

Demonstration of Tubercle Bacilli.—Maximal sensitivity in detecting tubercle bacilli in sputum has been found by injecting 2 cc. of non-modified sputum emulsified in physiological saline into a guinea pig treated preventatively with sulfamides. First, to determine the most sensitive preparation, sputum from 24 patients was injected into 72 guinea pigs. The first group of 24 pigs received 2 cc. of sputum emulsified with physiological saline (non-modified sputum); for group 2 the sputum was treated with 15 per cent sodium hydrate for twenty minutes at 37°C., then neutralized before injection; group 3 received a similar preparation, sulfuric acid being substituted for the alkali. In all cases the volume of injection was 2 cc. Group 1 showed unquestionably greater sensitivity in detecting bacilli; in no case was there any disparity in the results: no pig in group 2 or 3 developed tuberculosis without the corresponding pig in group 1 showing signs of the infection. Since the guinea pig is highly susceptible to the ordinary bacterial flora of the mouth, a means of decontaminating the sputum yet keeping it unmodified needed to be developed. Preventive sulfamidotherapy proved to be the answer to this problem: after injection of the non-modified sputum under the skin of the thigh, the guinea pig was fed 0.1 g. "Septoplax" daily for three days. Very satisfactory reduction in the mortality rate of the animals was thus obtained.—*Comparison des méthodes d'inoculation aux cobayes pour la*

recherche du bacille de Koch dans les crachats: Supériorité de l'inoculation du produit non modifié chez le cobaye traité par les sulfamides, F. Tison, *Ann. Inst. Pasteur*, February, 1947, 73: 186.—(P. Q. Edwards)

Tubercle Bacilli in Gastric Contents.—The gastric contents of 42 children were examined by direct smears, culture and animal inoculation; 34 were tuberculin reactors. Roentgenologically, mainly pulmonary and hilar tuberculosis was present, predominantly with discrete, and very rarely with disseminated, lesions. In 2 cases tubercle bacilli were found on direct smears, in 5 by culture and in 11 on inoculation. Positive results occurred only in tuberculin-positive children. In applying this method many possible errors, especially as to the anatomical source of the bacilli, must be excluded.—*The Research of the Bacillus in the Contents of the Stomach during Children's Tuberculosis*, S. Papaemmanuel, Sismogleion, *Archives of Tuberculosis (Greece)*, 1946, 2: 125.—(O. Pinner)

Bacteriological Diagnosis.—Failure to detect tubercle bacilli by direct microscopic methods, when clinical evidence or guinea pig inoculations demonstrate them, prompted a study of both clinical and bacteriological factors pertinent to this problem. Reasons given *a priori* for failure to detect bacilli when present in extremely small numbers are: (1) the acid-fast stains, (2) methods of homogenizing the sputum for examination and (3) Lowenstein's media, both old and new types. Bacillary colonies appeared slowly and in smaller numbers when inoculation was made on month-old cultures than when fresh material was used. When attempting to grow bacilli from material containing few organisms, the following procedures are recommended: slow homogenization with preliminary heating; centrifugation at high speed (5,000 r.p.m.) for one hour, inoculation of two guinea pigs with part of the sediment and inoculation on culture medium of the whole sediment. If these procedures are carefully followed, the

chances for recovering bacilli from bacilli-poor materials are greatly improved.—*De certaines difficultés dans le diagnostic bactériologique des tubercules paucibacillaires*, P.-J. Colekso, *Ann. Inst. Pasteur, February, 1947*, 73: 188.—(P. Q. Edwards)

Lipids, Albumin and Bacterial Growth.—Certain water-dispersible lipids enhance the growth of other bacteria, in particular, a certain micrococcus (strain C) recently isolated. The addition of crystalline serum albumin to this medium permits initiation of growth of minute inocula. The latter substance however did not increase appreciably the final density of the culture. A buffered basic medium containing hydrolysate of casein, glucose and yeast extract was used to observe the effect of different lipids and albumin. The basic medium alone gives a slow and scanty growth. In some of the tests a simple mineral solution was used, consisting of buffer salts and ammonium sulphate. Ferric chloride, glucose, enzymatic hydrolysate of casein, sodium stearate and oleate and serum albumin were added alone or in various combinations. The tubes were inoculated with micrococcus C or avian tubercle bacilli. To determine the effect of lipids and other substances on bacterial growth on solid (agar) medium, 1.5 per cent agar was added to the semisynthetic casein hydrolysate medium. Sodium oleate, ferric chloride and crystalline bovine albumin were added either separately or in combination. The long chain fatty acids have both inhibitory and stimulatory effects on the growth of tubercle bacilli and of micrococcus C. The toxicity of the fatty acids was reduced or abolished by (a) esterification, even when the resulting product was a water-soluble ester, and (b) addition of crystalline serum albumin to the culture medium; other proteins tested were inactive in this respect. Growth stimulation was obtained when certain long chain fatty acids were added in the form of their water-soluble esters, or in admixture with adequate amounts of serum albumin. Abundant growth of the micrococcus resulted from the addition of

oleic, linoleic, linolenic or arachidonic acid to a mineral medium containing glucose as sole source of carbon. Enhancement of growth of tubercle bacilli was obtained by adding to the medium a variety of fatty acids (saturated or unsaturated) even in the absence of glucose or of any other readily available carbon compound. These results suggest that long chain fatty acids can affect the growth of different microbial species through different metabolic channels and that, in order to study the mechanism of these metabolic and growth reactions, it is essential to use the fatty acids under conditions where they cannot manifest their toxic properties.—*The Effect of Lipids and Serum Albumin on Bacterial Growth*, R. J. Dubos, *J. Exper. Med.*, January, 1947, 85: 9.—(J. S. Woolley)

Vaccines in Experimental Tuberculosis.—Vaccines made from cultures of a strain of BCG and of a strain of virulent tubercle bacilli were killed by ultraviolet irradiation with the recently developed Oppenheimer-Levinsohn apparatus and compared with a live BCG vaccine and heat-killed vaccines of each of these strains. Two groups of guinea pigs received intraperitoneally three equal doses of the irradiated vaccines and of the live BCG vaccine, respectively, at weekly intervals; the guinea pigs in the third group received only a single dose of live BCG. Three weeks after the last vaccination all these animals, as well as two control groups of nonvaccinated animals received an intraperitoneal injection of a 15-day-old culture of the virulent bacilli. All animals were observed up to time of death and autopsied. The effectiveness of the different vaccines was evaluated on the basis of their ability to prolong the survival time over that of the control animals. Three doses of live BCG gave slight if any protection. The irradiated vaccine from the virulent tubercle bacilli, administered in three doses, was equal in effectiveness to a single dose of live BCG. Heat-killed bacilli, virulent or BCG, were ineffective, as was the ultra-violet-killed BCG.—*A Comparative Study of Live and Killed Vaccines in Ex-*

perimental Tuberculosis: A Preliminary Note,
B. J. Olson, K. Habel & W. R. Piggott,
Pub. Health Rep., February, 1947, 62: 293.—
(O. Pinner)

BCG in Sao Paulo.—In this collection of papers the developments are reviewed since BCG was introduced in Sao Paulo in 1926 to 1939, both in that city and elsewhere. Nearly 7,000 persons, including children and adults, had been vaccinated by 1937 at Sao Paulo and about 37,000 children and adolescents in the whole of Brazil. Approval is given to de Assis' statement that, while tuberculosis death rates in infants in a tuberculous environment vary from 8 to 30 per cent, they do not exceed 2.2 per cent in those vaccinated with BCG. BCG services are now in operation in most of the larger Brazilian cities, and especially at Rio, Sao Paulo, Sao Salvador, Belen, Recife, Belo Horizonte, Porto Alegre and Niehtheroi. At Rio over 52,000 children had been vaccinated by 1938, and the campaign has been intensified since that time. It is recommended that a similar effort be undertaken at Sao Paulo. Visiting nurses, of whom there are now an insufficient number, should help in this program. The subcutaneous route is now used almost exclusively. There is no question as to the innocuousness of the method. The Brazilian League against Tuberculosis has charge of this work under a contract with the National Department of Public Health, and manufactures the vaccine in its own laboratories.—*Trabalhos do Dr. Clemente Ferreira sobre a Vacina BCG em Sao Paulo, Publicações da Liga Paulista contra a Tuberculose*, 1942, pp. 61.—(A. A. Moll)

Hilum Tuberculosis.—In several patients, 30 to 60 years of age, roentgenograms revealed findings similar to those seen in epithelioid tuberculosis of children or young adults. The disease usually starts acutely with fever, chill, headache, cough and chest pain, sometimes with hemoptysis. The physical findings are scarce and not characteristic. The temperature frequently rises to more than 39°C.

it decreases after a few days and subfebrile temperatures may persist for some time. The erythrocyte sedimentation rate is usually high. There is usually a slight leucocytosis, in some cases with a relative lymphocytosis. Tubercle bacilli were never found in the sputum. The chest roentgenogram shows in all cases a shadow shaped like a cone or a pyramid, the apex being at the hilum and the basis at the periphery near the surface of the lung. Lymph node shadows of soft or calcified density are seen at the hilum or in the mediastinum. Sometimes there is a pleural effusion on the side of the pulmonary density. The diaphragm may be elevated and there may be an inspiratory shift of the mediastinum to the same side. It is believed that these findings are due to atelectasis in a circumscribed lung area caused by bronchial stenosis. The fever, the elevated sedimentation rate and the leucocytosis speak in favor of inflammatory processes being present at the same time. There is usually a high sensitivity to tuberculin. The frequent occurrence of such processes in the higher age groups is probably due to the war and post-war conditions, that is, poor nutrition, unusual aggravations and increased exposure to infection.—*Über ein gehäuftes Auftreten der von der Hilusgegend ausgehenden sog. Infiltrierungen im vorgerückten Lebensalter*, E. Zdansky & F. Wachtler, *Wien. klin. Wchnschr.*, September 20, 1946, 58: 541.—(G. C. Leiner)

Treatment of Tuberculous Tracheobronchitis.—Local treatment of tuberculous tracheal and bronchial lesions should be added to the general treatment of the patient and the treatment of the pulmonary disease. Bronchoscopic aspiration of secretions, cauterization of ulcers and granulations with diathermy or silver nitrate, and the application of adrenalin to the swollen mucous membranes are useful. In addition, the intratracheal instillation of penicillin several times a week, by lessening secondary infection and thinning the bronchial secretions, has been given to 14 of the 21 cases reported. Bronchoscopic observation has shown improvement in each of

those so treated with penicillin, results clearly superior to those given only silver nitrate, 2 of whom remained unimproved. Four cases are described in detail.—*Contribution à l'étude du traitement local de la tuberculose trachéo-bronchique*, J. Halle, *Laval méd.*, February, 1947, 12: 147.—(E. Bogen)

Laryngeal Tuberculosis.—The pathology of laryngeal tuberculosis is determined by the anatomy of the lymphatic apparatus of the larynx. The infection is propagated through canalicular, blood and lymphatic channels. Two types of edema are observed: (1) collateral or perifocal; (2) chronic, caused by tuberculous lymphangitis. Tuberculous tumors and lupus of the larynx are discussed. Changes in Poirier's gland, paresthesias and hoarseness are important for early diagnosis.—*Tuberculous Inflammations of the Larynx* (*Tuberkulosní záněty hrtanu*), Z. Jaros, *Lekarske Listy*, (Czech), December, 1946, 1: 580.—(O. Felsenfeld)

Calciferol in Tuberculosis.—In 20 cases of lupus vulgaris, the average duration of the disease was ten years. Practically every known form of treatment had been used previously. Large amounts of calciferol were administered either parenterally (600,000 units twice a week) or orally (150,000 units daily). Improvement began after three weeks in most cases. The rate of improvement was not a steady one but the results achieved were far better than with any other form of treatment. There were no remarkable changes in the blood calcium level. Later calciferol treatment was used in conjunction with local therapy and even better results were achieved. Two cases each of tuberculous cervical adenitis and of tuberculous tenosynovitis were then treated with excellent results. Toxic symptoms were noted in 50 per cent of cases, consisting of nausea, epigastric discomfort, depression and weakness. These were usually mild. There was an occasional flare-up of a quiescent tuberculous lesion. There was no evidence of renal damage.—*The Use of Calciferol in Tuberculous Conditions*, D. B.

Macrae, *Lancet*, January 25, 1947, 1: 185.—(A. G. Cohen)

Phlyctenular Conjunctivitis.—Tuberculosis was present in 27 out of 28 children (21 females and 7 males between 11 months and 15 years of age) with phlyctenular conjunctivitis. One child had *tabes mesenterica*, 3 tuberculous cervical lymphadenitis and 23 cases showed roentgenological evidence of pulmonary tuberculosis. The latter group consisted of 17 active and progressive lesions, including 3 of the fibroscous type, and only 6 apparently healed or quiescent lesions. In 10 cases the lesions of the eye and of the lung were homolateral; of the 6 cases with bilateral lung lesions, 2 had only one eye affected; 2 of the 3 cases with extrapulmonary tuberculosis had bilateral lesions. There were 10 cases with known tuberculous contact; 7 children had had contact with patients with chronic cough of unknown etiology. In one family, 4 children had phlyctenulosis; when the eldest of the children was hospitalized after a severe hemoptysis, the eye lesions of the other 3 cleared up within ten days.—*Phlyctenular Conjunctivitis: A Clinical and Radiological Study of 28 Cases*, I. Mirvish & D. Hilson, *Clin. Proc. (Cape Town)*, November, 1946, 5: 388.—(O. Pinner)

Tuberculosis Conjunctivitis.—Tuberculosis of the conjunctiva is uncommon; primary lesions are even more rare. Except for a Scandinavian series of 40 cases, reported in 1936, only isolated case-reports have been published. The diagnosis of a primary lesion is based upon the absence of a demonstrable lesion elsewhere, the unilateral character of the process and the involvement of regional nodes. The methods of inoculation and the types of lesions are described. One case of primary tuberculosis of the conjunctiva in a 10-year-old child is described. Diagnosis was made by biopsy.—*Primary Tuberculosis of the Conjunctiva*, A. A. Goldfarb & I. Seltzer, *Am. J. Dis. Child.*, August, 1946, 72: 211.—(W. H. Oatway, Jr.)

Tuberculous Splenomegaly.—Only about 100 cases have been reported in the literature, and only 5 were less than 10 years of age. A Negro boy, 11 years of age, is reported whose complaint was stiffness in the back. X-ray abnormalities at one apex were transient. A tuberculin patch-test was negative, as were two Mantoux tests (1:100,000 and 1:1,000). Leucopenia and thrombocytopenia were present. Banti's disease was diagnosed and the spleen was removed. It weighed 700 g., was adherent to the posterior wall (the cause of pain) and consisted mainly of epithelioid proliferation. The blood changes reverted to normal after operation.—*Tuberculous Splenomegaly in Children*, C. R. Dietz, *Arch. Pediat.*, April, 1946, 63: 168.—(W. H. Oatway, Jr.)

paste. At the periphery the brain tissue was studded with innumerable hemorrhages. Microscopically the intracerebral vessels of the frontal lobe showed extensive hyalin fibroid degeneration. No giant cells or tubercles were seen anywhere and only rarely did small clumps of epithelioid cells occur. Acid-fast bacilli were extremely rare. In these two cases it was evident that thrombosis played the chief rôle in the production of hemorrhage. The vascular fibrinoid degeneration of Askanaazy was present in the subintimal zone and media of the involved vessels, more frequently in intracerebral than in meningeal vessels.—*Gross Cerebral Hemorrhage and Vascular Lesions in Acute Tuberculous Meningitis and Meningo-Encephalitis*, J. W. Goldzicher & J. R. Lisa, *Am. J. Path.*, January, 1947, 23: 153.—(J. S. Woolley)

Vessels in Tuberculous Meningitis.—Two cases of acute tuberculous meningo-encephalitis with gross hemorrhages and extensive vascular lesions of an unusual nature are reported, one was a 36-year-old Negress, who had signs of cerebral irritation and whose cerebro-spinal fluid, suggested tuberculous, although tubercle bacilli were not found. Death occurred in coma on the fifteenth hospital day. A postmortem examination showed that the entire base of the brain was covered by a dense, yellow, adherent exudate. On the surface were many minute, tubercle-like nodules. On sectioning, the brain showed areas of petechial hemorrhage. The meningeal vessels were extensively involved. Acid-fast bacilli were found in the adventitia or media of the affected areas. Of great interest was the hyaline-fibrinoid degeneration of Askanaazy affecting the media and intima of the smaller arteries and arterioles. The second case was a female eretin dwarf, 48 years old, whose physical examination and spinal fluid were suggestive of meningeal irritation. Death occurred twenty hours after admission. Examination of the brain showed but little exudate over the base. The frontal lobes were extremely soft and bluish. These lobes were almost completely destroyed and had the appearance of a soft hemorrhagic

Agnesis of Lung.—The congenital absence of a right lung was diagnosed in an otherwise normal and asymptomatic infant 8 months of age. The criteria were similar to those generally accepted. Only 4 of the 41 cases previously noted in the literature were diagnosed during life.—*Agnesis of the Lung*, A. Wideman & C. H. Peters, *J. Pediat.*, February, 1946, 28: 204.—(W. H. Oatway, Jr.)

Pneumothorax in Newborn.—The condition is rare, but probably unrecognized at times. It requires an X-ray examination for diagnosis, since the signs and symptoms are not always prominent. Trauma at birth is a probable major cause. It has been suggested that the term be limited to those cases which are recognized within four to five days after birth. One case with recovery is described. Conservative treatment is recommended, with aspiration only for the more severe form.—*Spontaneous Pneumothorax in the Newborn*, E. P. Scott & C. C. Rotondo, *Am. J. Dis. Child.*, August, 1946, 72: 207.—(W. H. Oatway, Jr.)

Spontaneous Pneumothorax.—This condition is seen predominantly in healthy young men without a history of previous pulmonary

disease. Twenty-four such cases are described. The pathogenesis is believed to be rupture of a valve vesicle or pleural or subpleural bleb. The clinical picture is usually one of sudden onset of unilateral pain and dyspnea. The average reëxpansion time is five weeks. The prognosis in the uncomplicated case is excellent.—*Simple Spontaneous Pneumothorax in Apparently Healthy Individuals*, R. F. Nichaus, *Am. J. Roentgenol.*, January, 1947, 57: 12.—(J. E. Farber)

Bronchoscopy in Newborn.—Aspiration through the bronchoscope is recommended for those cases of atelectasis in the newborn in which bronchi are obstructed by secretions. All other possible causes of congenital atelectasis should be ruled out before the procedure. Coarse moist râles are usually present in suitable cases. Conservative treatment is advisable only if effective and while safe. The series includes 23 cases, 19 of which had been premature deliveries. The results were excellent in 15 cases. Eight infants were bronchoscoped without establishing a diagnosis; all eventually died; only 2 of them were found to have congenital atelectasis. Bronchoscopy is tolerated well by infants. The secretions are usually loose and the bronchial surfaces may occasionally be cohesive.—*Atelectasis of the Newborn: Treatment by Bronchoscopic Drainage*, H. P. House & H. Owens, *J. Pediat.*, February, 1946, 28: 207.—(W. H. Oatway, Jr.)

Chylothorax in Infancy.—A case of spontaneous chylothorax in an infant, with recovery, is reported. Twelve other cases in the literature are reviewed. Aspiration and a low-fat diet are recommended. The prognosis for life and spontaneous healing is excellent.—*Spontaneous Chylothorax in Infancy*, E. H. Watson & L. F. Foster, *Am. J. Dis. Child.*, July, 1946, 72: 89.—(W. H. Oatway, Jr.)

Penicillin Inhalation.—Therapy was given for three to seven days in pneumococcus pneumonia, for three to four weeks in streptococcus or staphylococcus pneumonia and for

three days to three weeks in bronchial asthma; in bronchiectasis, treatment was given for seven days in preoperative cases and for four to six weeks in medically treated cases. The sodium or calcium penicillin salt was used; doses of 25,000 units dissolved in 1.0 cc. of saline were given six to eight times a day at intervals of three hours. The calcium salt was found to be less irritating. A vaponefrin nebulizer was used. Oxygen delivered at the rate of 5 to 7 liters per minute was found to aerosolize 1.0 cc. of penicillin solution in fifteen minutes. Good blood levels were obtained; these are not considered important. Prompt cures were obtained in 9 cases of pneumococcus pneumonia. Inhalation therapy is suggested as a supplementary treatment in cases of streptococcus, pneumococcus and Friedlander's pneumonia. Results in 22 cases of infective bronchial asthma were generally disappointing, although the susceptible organisms disappeared promptly from the sputum and there was an occasional good result. In 30 cases of bronchiectasis, inhalation therapy given for six weeks, with treatments preceded by postural drainage, resulted in great improvement. Good results were obtained with four weeks of therapy in 11 cases of aerobic lung abscess; surgical therapy was thus averted in most cases. Results in cases of anaerobic abscess were poor. Dramatic results were obtained in 6 cases of acute laryngo-tracheobronchial edema. In cases of pulmonary emphysema and emphysematous blebs, treatment had previously consisted of inhalation of 50 per cent oxygen and aerosolized bronchodilators. With added penicillin good results were obtained in 6 cases.—*Penicillin Inhalation Therapy*, M. S. Segal & C. M. Ryder, *New England J. Med.*, January 28, 1947, 236: 182.—(A. G. Cohen)

Staphylococcus Pneumonia.—A series of 40 young children with staphylococcus (suppurative) pneumonia were seen during the past fifteen years. Sepsis with metastatic pulmonary abscesses is excluded; only bronchogenic pneumonia is included. A pure culture from the lungs or pleural space ob-

tained at operation, autopsy or aspiration is the only admissible evidence. The clinical categories are divided into acute and chronic cases; diffuse and localized suppuration; and those with or without pleural involvement. Clinically, the acuteness of pleural involvement is notable, as is the tendency of apparently healed pneumonitis to recur later as a chronic abscess. Roentgenologically, areas of rarefaction often suddenly appear in the consolidation. Sulfonamide therapy has been disappointing; results from penicillin have usually been brilliant. The abrupt and dangerous pleural complications should be treated at once by closed drainage, which may be curative, especially in conjunction with penicillin. If it is not, open drainage (near the bronchial fistula) should be done later, possibly followed by a fat graft if closure does not occur. A pulmonary abscess may require surgery, preferably a one stage operation. Penicillin has had scanty use in this series. Pleural complications occurred in 92 per cent, broncho-pleural fistula in 70 per cent and a fatal outcome in 37.5 per cent.—*Staphylococcus (Suppurative) Pneumonia in Infancy and in Childhood and Its Surgical Aspects*, S. Blumenthal & H. Neuhauf, *Am. J. Dis. Child.*, December, 1946, 72: 691.—(W. H. Oatway, Jr.)

Interstitial Pneumonia.—Boisset did 875 autopsies on children who died of pneumonia during the last five years. This represents 34.8 per cent of all autopsies during that time; 5 per cent were lobar pneumonias, 95 per cent were atypical bronchopneumonias. Of the latter, 15 per cent were interstitial bronchopneumonias; 73.6 per cent of the interstitial pneumonias occurred after whooping cough and 26.4 per cent after measles. Whooping cough pneumonia caused 11 per cent of all the deaths in the group of 875 children, but it is believed that a filtrable virus was directly responsible for the pneumonia and not *Hemophilus pertussis*. An infiltration of mononuclear cells was found in the walls of the alveoli, in the interlobular septa and in the perivascular and peribronchial tissue. Often, small vesicles of emphysema were observed on the surface of the lungs. In the most typical cases numerous isolated foci of grey hepatization surrounded by intense hyperemia were found. Sometimes, a lobular caseous pneumonia could have been mistaken for tuberculous. One case of interstitial pneumonia with giant cells of Hetch, an extremely rare condition, was found. Although this is generally due to the virus of measles, in this case only a general vitamin deficiency was found on autopsy and no history of acute infection could be obtained. Interstitial pneumonia can be the cause of sudden death in children.—*Estudio anatomopatológico de las neumonías intersticiales*, G. Boisset, *Rev. del Hospital del Niño*, June, 1946, 8: 180.—(W. Scrimley)

Chemotherapy of Bronchitis.—Congenital cystic fibrosis of the pancreas is associated with nutritional deficiency, intestinal dysfunction and chronic respiratory infection in young children. Dietary therapy is of value in preventing pulmonary lesions, but of little value after they occur. The general pattern of lung infection is uniform: a dry cough occurs, usually between the second and sixth month of life; scanty fever; no X-ray findings; cough becomes more severe; weight loss occurs; the chest becomes emphysematous; coarse râles are heard; finally the chronicity belies whatever wrong diagnosis has been made. Signs of asphyxia occur, the X-ray often shows 'snowflake' areas, viscid sputum is present and the patient may abruptly die. Occasionally the onset is delayed, with recurring 'colds', and the child may be five years of age before cyanosis and other processes begin. Hemolytic *Staphylococcus aureus* was found in 13 of 15 cases in this series. Necropsy shows a combination of acute and chronic changes. The basic change is a chronic bronchitis with peribronchial fibrosis and occasional tubular dilatation; the acute lesion is a suppurative bronchitis. There may be emphysema, lobular pneumonia and atelectasis. Sulfonamides are effective in prophylaxis and treatment of intercurrent upper respiratory infections, but not for the suppurative bronchitis. Peni-

illin is valuable in cases with a sensitive organism. Aerosol (20,000 U., seven times a day) is best for patients over one year of age; intramuscular doses should be added where parenchymal involvement is suspected; and the latter method alone should be used for infants of less than one year. Administration of the aerosol by nasal catheter is effective but difficult in infants. In early infancy prognosis is poor. A late onset, good general condition, and the use of dietary measures plus penicillin combine for the best prognosis.—*Celiac Syndrome: IV. Chemotherapy in Infections of the Respiratory Tract Associated with Cystic Fibrosis of the Pancreas: Observations with Penicillin and Drugs of the Sulfonamide Group, with Special Reference to Penicillin Aerosol*, P. E. A. di Sant'Agnese & Dorothy H. Andersen, *Am. J. Dis. Child.*, July, 1946, 72: 17.—(W. H. Oatway, Jr.)

Pneumatocele in Childhood Pneumonias.—The appearance of a 'cavity' in the X-ray films of children with pneumonia is common. These rarefactions are benign emphysematous bullae and must be differentiated from a true excavation; they have an excellent prognosis. They are produced by a check-valve mechanism in the swollen bronchial mucosa. Differential diagnosis and classification of pulmonary cysts are discussed. Complications (even rupture) are rare. Seven cases with one or more pneumatoceles, found in a series of 50 cases of pneumonia, are described. Fluid levels were present in 5 of the 7. The duration of the rarefaction is variable, often brief. All cleared spontaneously and all patients recovered.—*Pneumatocele during the Course of Pneumonia in Children*, J. R. Almklov & A. Hatoff, *Am. J. Dis. Child.*, November, 1946, 72: 521.—(W. H. Oatway, Jr.)

Eosinophilic Lung and Ascariasis.—Three syndromes have been described in recent years which include eosinophilia and pulmonary changes: Loeffler's syndrome, tropical eosinophilia ('eosinophilic lung') and pulmonary ascariasis. A case is presented which apparently includes all three. A Negro child,

age 2 years, who had lived in Florida was found to be toxemic, febrile, to have a cough and to have emeses and diarrhea. He had eaten considerable amounts of dirt, had had eczema and possibly pneumonia and whooping-cough. The liver was moderately enlarged. X-ray films of the lungs showed peritruncal accentuation at the bases. The white count varied from 21,000 to 117,000, with 31 to 82 per cent eosinophils. A liver biopsy showed multiple tiny areas of focal necrosis. Episodes of edema of the lips occurred. Methionine was used to protect the liver. He vomited a single male ascaris. Hexylresorcinol was prescribed, and his symptoms, X-ray changes, hepatomegaly, focal necroses and leucocytosis returned to normal. The percentage of eosinophils and the sedimentation rate remained elevated.—*Chronic Eosinophilia: Report of a Case with Necrosis of the Liver, Pulmonary Infiltrations, Anemia, and Ascaris Infestation*, Josephine G. Perlingiero & P. György, *Am. J. Dis. Child.*, January, 1947, 73: 84.—(W. H. Oatway, Jr.)

Cress for Catarrhal Bronchitis.—While the use of common cress (*Lepidium sativum*) in bronchial processes has long been known, attention is again called to the drug because of its availability in Brazil. The author has confirmed its value as an expectorant and especially as an aid in the treatment of acute and chronic bronchitis. The active principle is lepidin, an iodine-containing glucoside.—*O Emprego do Mastruco nas Bronquites Catarrais*, D. Fonseca de Carvalho, *Clin. Tisiol.*, April-June, 1946, 1: 38.—(A. A. Moll)

Anomalous Pulmonary Veins.—Anomalous pulmonary veins have been classified in two groups; cases in which only a part of the blood from the lungs entered the right atrium by direct or indirect routes; and cases in which all the pulmonary blood reached the right atrium. The latter situation is believed to be incompatible with life. A minimum of 50 per cent of the aerated blood must reach the left atrium to sustain life; with 75 per cent there will be no recognizable cardiorespiratory

symptoms. A case of congenital malformation of the heart and aorta with drainage of the pulmonary veins into the ductus venosus is reported. A male child was delivered weighing 10 lbs. At the time of birth the child was cyanotic and had the umbilical cord wrapped twice around his neck. At thirty hours the infant suddenly became dyspnoic and cyanotic and died on the twelfth day in severe respiratory distress. The postmortem examination revealed a cyanotic infant in whom all organs were normal except for anomalies of the heart, aorta and pulmonary veins. The left side of the heart was very small and no blood vessels entered the left atrium. The aorta exhibited a coarctation at a point just distal to the left subclavian artery. The pulmonary veins united near the hilus of each lung to form two trunks. These fused in the midline posterior to the heart to form a single vessel which passed through the diaphragm close by the inferior vena cava to empty into the ductus venosus just above the obliterating umbilical vein. The ductus venosus was still patent and communicated freely with the inferior vena cava. Blood, therefore, oxygenated in the lungs had to pass through the common trunk formed by the pulmonary veins into the ductus venosus and thence into the inferior vena cava, with a probable backflow into the umbilical vein and the adjacent portal vein. Oxygenated blood was thus mixed with the purely venous blood of the inferior vena cava. As it entered the right atrium the blood was again mixed with the purely venous blood of the superior vena cava. From the right atrium the mixed blood passed into the pulmonary circuit, through a patent ductus botalli into the peripheral circulation, through an open foramen ovale into the small left atrium, and through a small intraventricular defect into the left ventricle. The mixed blood from the left atrium and left ventricle passed into the aortic arch and its vessels, encountering resistance at the point of coarctation. No organ or part of any organ received purely arterial blood. Only one somewhat similar case was found in the literature although several cases have been reported with complete or incomplete pulmonary venous drainage into vessels inferior to the right atrium. (Illustrated.)—*Drainage of the Pulmonary Veins into the Ductus Venosus Arantii: Report of a Case*, W. H. Mehn & F. E. Hirsch, *Am. J. Path.*, January, 1947, 23: 125.—(J. S. Woolley)

LATE RESULTS OF THORACOPLASTY¹

RICHMOND DOUGLASS

The aim of treatment in tuberculosis is to establish control of the disease, and to enable the patient safely to resume active life. It is, therefore, important to evaluate a procedure, not only at the time of discharge from treatment, but at intervals thereafter. The rôle of thoracoplasty has been presented repeatedly from the standpoint of operative results, but presentations such as that of Skinner, Macpherson and Allen (1) in 1941, with review of results covering periods of five to fifteen years after operation, have been infrequent.

Interest in the surgical program at the Hermann M. Biggs Memorial Hospital stimulated a review of all thoracoplasty patients and a further study of the patients operated upon at the Mount Morris Tuberculosis Hospital. Time has not permitted a review of the cases treated at the two remaining district hospitals in the State, but the surgical approach and volume of work was comparable for the period covered. It is planned ultimately to study all cases, and to present a complete report at a later date.

For the purpose of this presentation, those patients operated upon in the period 1936 to 1941, inclusive, were reviewed as to their status in the fifth year after completion of their surgical treatment. In the majority this surgery consisted of a multiple-stage thoracoplasty, but in others secondary procedures such as revisions, Schede operations, or lobectomies were done. The period covered represents the early years of operation of the two hospitals. Under the circumstances, an effort was made to carry out surgery on patients who were reasonably good risks, although poor risks were not entirely excluded. On the other hand, the patients had had a trial of other forms of treatment, and early, elective thoracoplasties are not represented. It was the accepted policy that the contralateral lung, if diseased, must be stable (usually for six months), or be under control by pneumothorax. Specific tabulation of the patient's status both as a surgical risk and also as regards the prognosis for controlling his tuberculosis is not possible, as the indications had not been clearly defined, and the records are inadequate for this purpose. The records for the next five years will make such a review possible.

Comment is also required concerning the postoperative care. It was conservative, with an initial period of six months' bed-rest followed by cautious increases in activity, the typical case at Ithaca spending a year and a half in the hospital after completion of surgery.

The status at the fifth year has been stated as Good, Improved, Unsatisfactory or Dead.

1: The "Good" category requires that sputum be absent or microscopically negative, that the X-ray films show a stable lesion with cavity closed, that there be no sinus of the chest wall, and that the patient be able to lead an active life, though with reasonable

¹ From the Hermann M. Biggs Memorial Hospital, Ithaca, New York.

limitations. If sputum studies had been carried out consistently on the basis of cultures such data would be more valuable, but many of the patients were referred for surgical treatment, and such reports were not available.

2: The "Improved" group includes those with marked decrease in sputum and its bacillary content, or with a small chest wall sinus in the case of empyema patients. These patients are in most instances self-supporting.

3: The "Unsatisfactory" group includes those with active disease or serious chest wall infection and in need of hospital care.

4: "Dead" includes all deaths from whatever cause.

The total group includes 121 patients, subdivided into two subgroups, Pleural and Parenchymal. The pleural group comprises the patients upon whom the operation was done for conditions related to the pleura, the sputum being negative on concentration at the time of the operation. There were 19 such cases. The parenchymal group comprises the patients upon whom the operation was done for active parenchymal disease, including endobronchial disease. This group included 102 cases.

It is of some interest to review the source of the follow-up information, which suggests that more emphasis might be placed on this phase of the tuberculosis program. The records were based upon:

1. Reference to the Hospital case records.....84
 2. Data secured from referring sanatoria or from health officers.....19
 3. Personal letters to patients or their physicians15
- Three patients could not be followed.

Despite the scattered sources of information, it is felt that the data presented are reliable, within the limits indicated by their sources.

Table 1 shows the distribution of the cases and the results as related to the subgroups. No deaths occurred in the pleural group.

Table 2 shows the sex distribution. There is a slight predominance of females and a slightly better result for this sex.

Table 3 indicates whether the cases were referred from other sanatoria for surgery. It is of interest to note that, among the referred cases, there is a higher percentage of pleural problems.

Graphs 1 and 2 give the five-year status by sex and age. Five patients were under 30 and 3 over 50, reflecting the attitude toward age as a factor in the selection of cases.

The various indications in the pleural group are presented in table 4. It is noteworthy that tuberculous empyemata are the major problem. The fact that 2 pneumothorax patients had pyogenic empyema is important as reflecting one hazard of long continued pneumothorax.

The parenchymal group requires more detailed study. Certain facts are presented, including the type of operation performed, results in relation to cavity size and to time of sputum conversion, the status at discharge and the cause and time of death.

As shown in table 5, the standard multiple-stage, partial or total, thoracoplasty

was used in 55 cases. The same basic procedure was supplemented by an apicolysis in an additional 23 cases. Monaldi suction drainage had been used in only 4 patients. In each instance this procedure preceded the thoracoplasty. The fourth subgroup includes 6 revisions of thoracoplasties done elsewhere, and a

TABLE 1

Fire-year status of 121 thoracoplasty patients discharged from Biggs Memorial Hospital and Mt. Morris Tuberculosis Hospital

INDICATION	TOTAL	GOOD	IMPROVED	UNSATISFACTORY	LOST	DIED
Pleural disease.....	19	16	1	2	—	—
Parenchymal disease.....	102	69	6	10	3	14

Good = Arrested or better; no chest wall infection.

Improved = Scanty sputum; few bacilli; able to work; slight or no chest wall infection.

Unsatisfactory = Active disease in lung or chest wall; in need of hospital care.

TABLE 2

Fire-year status of 121 thoracoplasty patients by sex and indication for operation

INDICATION	SEX	TOTAL	GOOD	IMPROVED	UNSATISFACTORY	LOST	DIED
Pleural	M	10	9	—	1	—	—
	F	9	7	1	1	—	—
Parenchymal	M	46	28	3	5	2	8
	F	56	41	3	5	1	6

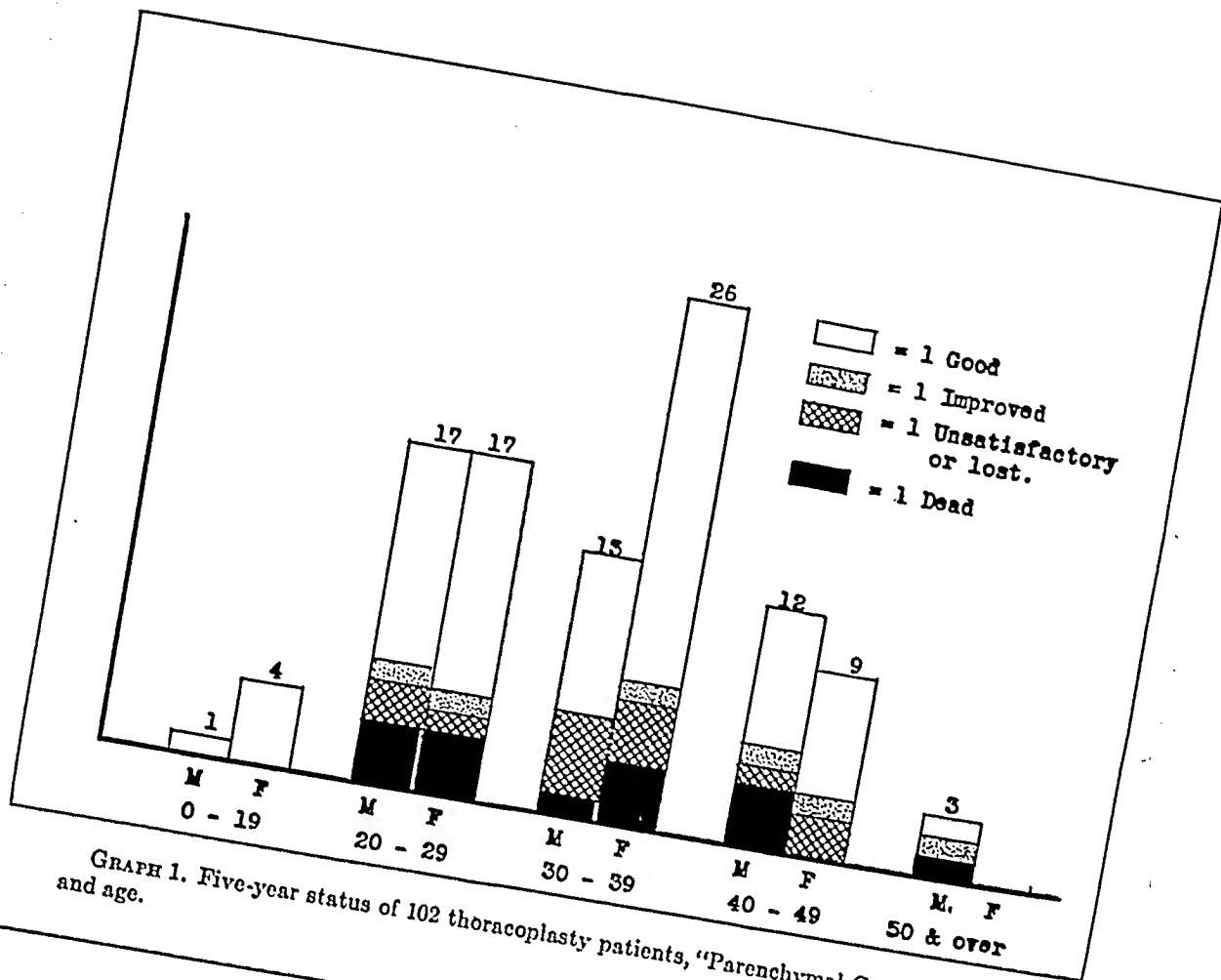
TABLE 3

Fire-year status of 121 thoracoplasty patients by origin of patient and indication for operation

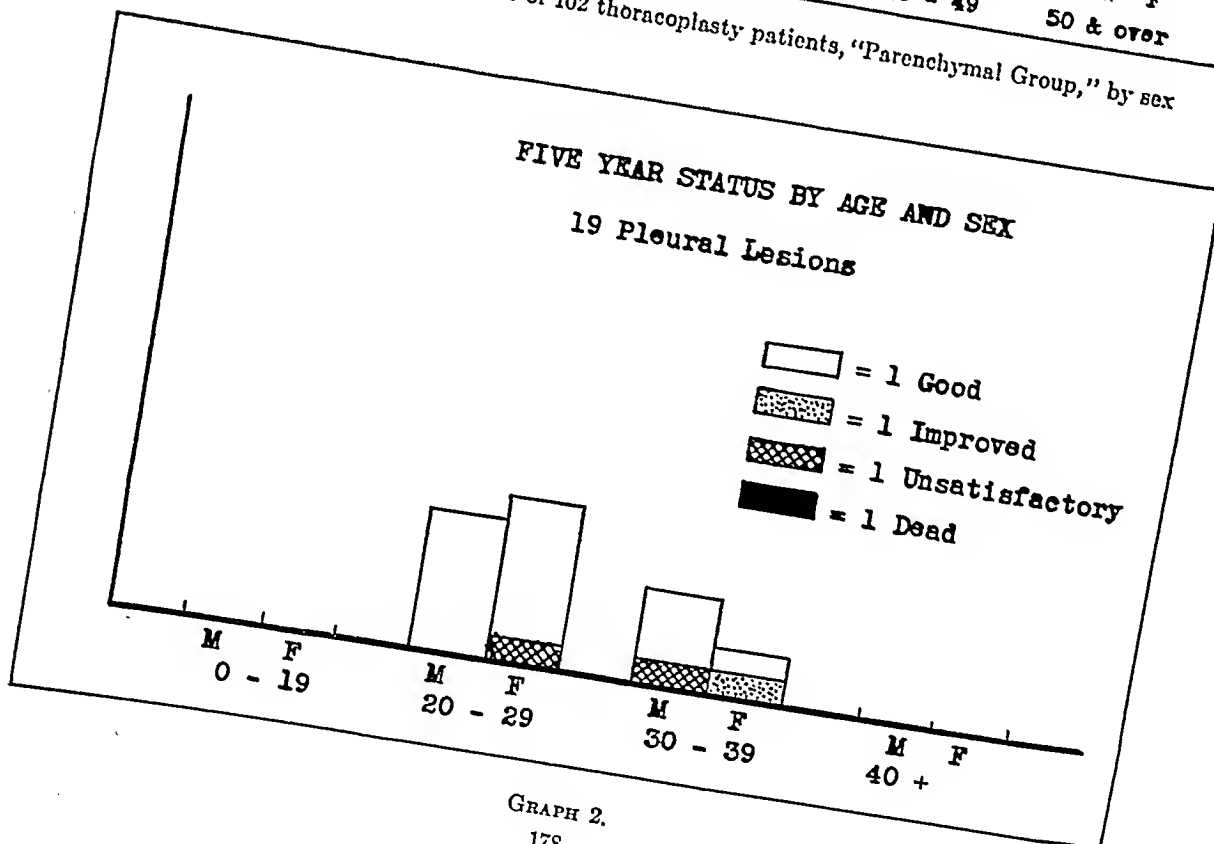
INDICATION	SOURCE	TOTAL	GOOD	IMPROVED	UNSATISFACTORY	LOST	DIED
Pleural	District	12	11	—	1	—	—
	Referred	7	5	1	1	—	—
Parenchymal	District	85	58	5	10	3	9
	Referred	17	11	1	—	—	5

few atypical procedures, including some myoplastic thoracoplasties. The group of 6 patients in whom the planned procedure remained uncompleted includes postoperative deaths, those having spreads of disease and those who could not tolerate further major surgery.

Table 6 shows the distribution of cases in relation to the size of cavity. This criterion is given instead of the usual classification into minimal, moderately advanced and far advanced. The size of cavity was determined on the basis of



GRAPH 1. Five-year status of 102 thoracoplasty patients, "Parenchymal Group," by sex and age.



GRAPH 2.

the preoperative X-ray film. Patients with recognized endobronchial disease account for 4 of the 5 patients with no cavity.

TABLE 4

Status of 19 patients five years after completion of operation for pleural problems

TYPE OF PROBLEM	TOTAL	GOOD	IMPROVED	UNSATIS- FACTORY	LOST	DIED
Tuberculous empyema, purulent..	11	9	1	1	—	—
Mixed empyema.....	3	2	—	1	—	—
Nontuberculous pyogenic empyema.....	2	2	—	—	—	—
Inexpansile lung.....	3	3	—	—	—	—
Total.....	19	16	1	2	—	—

TABLE 5

Five-year status, according to type of operation, of 102 patients with parenchymal lesions

TYPE OF OPERATION	TOTAL	GOOD	IMPROVED	UNSATIS- FACTORY	LOST	DIED
All operations	102	69	6	10	3	14
Partial and total	55	39	5	3	1	7
Apicolytic	23	19	1	1	1	1
With Monaldi drainage	4	4	—	—	—	—
Other types of operation	14	7	—	4	—	3
Planned procedures not completed —all types	6	—	—	2	1	3

TABLE 6

Five-year status, by size of cavity at operation, of 102 thoracoplasty patients

CAVITY SIZE	SEX	TOTAL	GOOD	PER CENT GOOD	IMPROVED	UNSATIS- FACTORY	LOST	DIED
No cavity	M	1	1)	60	—	—	—	—
	F	4	2)		1	1	—	—
Under 2 cm.	M	16	11)	76	2	—	—	3
	F	13	11)		—	—	1	1
2 to 4 cm.	M	11	4)	62	—	3	1	3
	F	18	14)		1	3	—	—
4 cm. and over	M	18	12)	67	1	2	1	2
	F	21	14)		1	1	—	5

The most significant fact in the table is the 67 per cent of good results in patients with cavities over 4 cm. in diameter. This is in sharp contrast to the results in comparable cases as regards cavity size treated by pneumothorax in

this Hospital, and suggests that thoracoplasty should be the treatment of choice in these cases.

Table 7 is of interest in that 50 per cent of the conversions occurred within six months. It is also of interest that, in the group in which conversion took place within six months, each of the 3 listed as "Unsatisfactory" at five years is nega-

TABLE 7
*Five-year status of 102 thoracoplasty patients by time of sputum conversion**

TIME OF CONVERSION	TOTAL	GOOD	IMPROVED	UNSATIS- FACTORY	LOST	DIED
Negative preoperatively.....	6	6	—	—	—	—
Less than six months.....	48	43	1	3	1	—
Six months to one year.....	12	9	1	1	—	1
Over one year.....	12	11	—	—	1	—
No conversion in five years....	24	—	4	6	1	13
Total.....	102	69	6	10	3	14

* Conversion is defined as sputum negative on standard concentration technique for at least six months.

TABLE 8
Status, five years after thoracoplasty, of 102 patients, by status on discharge

STATUS ON DISCHARGE	TOTAL	GOOD	IMPROVED	UNSATIS- FACTORY	LOST	DIED
Arrested and apparently arrested	44	37	2	2	2	1
Quiescent, with consent	13	11	1	1	—	—
Transferred to referring hospital	16	14	1	—	—	1
Quiescent, without consent	10	7	2	1	—	—
Active at discharge	4	—	—	3	1	—
Still in Hospital	3	—	—	3	—	—
Died in Hospital	12	—	—	—	—	12
Total	102	69	6	10	3	14

tive: one at seven years after contralateral thoracoplasty; one at seven years after a period of rest for contralateral disease; and a third, at eight years after closing the cavity. These patients showed an ability to heal their disease. On the other hand, only one of the 43 "Good" cases has had a reactivation of disease. The high percentage of late good results in those cases who had a delayed conversion of sputum (over one year) suggests that slow conversion is not necessarily a cause for concern. The longer hospital care afforded these patients undoubtedly contributed to the stability of the healing.

The five-year status with relation to condition on discharge (table 8) is important. Those discharged "with consent" classified as quiescent were negative with 2 exceptions, but did not have the exercise qualifications for "apparently arrested." Those transferred went to their referring sanatoria and received

TABLE 9

Causes of death of 14 patients, by interval between thoracoplasty and death

CAUSES OF DEATH	INTERVAL BETWEEN THORACOPLASTY AND DEATH			
	0-60 days	2-6 months	6-12 months	Over 1 year
Postoperative primary procedure	1	—	—	—
Progressive pulmonary tuberculosis	—	—	—	8 4, 1 to 2 years 1, 2 to 3 years 3, 3+ years
Spontaneous pneumothorax contra-lateral side	2	—	—	—
Following lobectomy	1	—	1	—
Following revision	1	—	—	—
Total — 14	5	—	1	8

TABLE 10

Comparative late results after thoracoplasty

AUTHOR	TOTAL	GOOD	IMPROVED AND UNSATISFACTORY	LOST	DIED
8-16 years	50	29	2	—	19 (14 tuberculous)
Skinner	100%	58%	4%	—	38% (28% tuberculous)
5-8 years	50	32	5	1	12
Skinner	100%	64%	10%	2%	24%
5 years	102	69	16	3	14
Douglass	100%	69%	16%	3%	14%

Skinner *et al.*—St. Johns, New Brunswick.

Douglass—Biggs Hospital, Ithaca, New York.

convalescent care which was adequate. The 73 patients discharged as arrested, quiescent "with consent," or transferred showed 62, or 85 per cent, in the good status at five years. As of the present, there have been no other deaths, one has had a breakdown, and 2 have reverted to a "good" status.

The consideration of the causes of death (table 9) shows a mortality of 3 per

cent after the primary procedure in the 102 patients with parenchymal disease. The secondary procedures were the cause of death in 3 cases, but this group is small, and does not warrant any conclusions.

Table 10 presents a comparison of our figures with those of Skinner and associates of St. John's, New Brunswick. Their early group (1924-1932) consisted of operations of the Sauerbruch type, while the second group (1932-1936) represents the early use of the modern type of operation. It is regretted that their results are not stated at five, ten and fifteen-year intervals, which would make comparison of groups more exact.

Thoracoplasty is a valuable procedure in the treatment of cases of advanced tuberculosis. This study shows that in 70 per cent of the cases treated by thoracoplasty good results were obtained five years after completion of surgery.

In terms of percentages and in view of the type of disease treated, thoracoplasty gives encouraging results at a five-year follow-up. Comparison with other types of treatment will be possible only when follow-up studies on comparable cases are reported.

SUMMARY

The value of thoracoplasty in treating tuberculosis has usually been presented from the standpoint of early operative results. Evaluation of the procedure after the lapse of five, ten or fifteen years has been infrequent.

A group of 121 patients operated during the period of 1936 to 1941, inclusive, was studied and the status in the fifth year after completion of surgery tabulated. The five-year status is expressed in terms of "good," "improved," "unsatisfactory" or "dead" and these terms are defined.

Nineteen cases presented problems related to the pleura, the sputum being negative on concentration at the time of operation. The five-year status was good in 16.

One hundred and two cases were operated upon for parenchymal disease, including endobronchial tuberculosis. The five-year status in the parenchymal group was good in 69.

Death occurred within sixty days in 3 cases after standard thoracoplasty and in one case after a revision operation.

It is urged that late results be reported on the basis of the status at five-year intervals.

SUMARIO

Resultados Tardíos de la Toracoplastia

El valor de la toracoplastia en el tratamiento de la tuberculosis ha sido habitualmente descrito desde el punto de vista de los resultados operatorios tempranos, siendo rara la evaluación del procedimiento a plazos de 5, 10 o 15 años.

Un grupo de 121 enfermos operados durante el período de 1936 a 1941, inclusive, fué estudiado, tabulándose su estado a los 5 años de haberse terminado la

intervención y clasificándose en términos de "bueno," "mejorado," "poco satisfactorio" o "muerto," después de definir los primeros tres términos.

Diecinueve casos presentaban problemas relacionados con la pleura, siendo negativo el esputo con la técnica de la concentración en la fecha de la operación. El estado a los 5 años fué bueno en 16.

Ciento dos casos fueron operados por enfermedad del parénquima, comprendiendo tuberculosis endobronquial. En este grupo el estado a los 5 años resultó bueno en 69.

Sobrevinieron muertes en término de 60 días en 3 casos consecutivamente a una toracoplastia clásica y en un caso tras una operación correctora.

Abógase porque se comuniquen los resultados tardíos de la toracoplastia a base del estado a plazos quinquenales.

The author wishes to acknowledge his indebtedness to Mr. E. B. Bosworth for assistance in the statistical studies and to Mary E. Thompson for constructive criticisms.

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TUBERCULOUS PLEURISY WITH EFFUSION¹

An Analysis of 215 Cases Hospitalized at an Army Chest Center

IRWIN G. KARRON² AND ROBERT K. PURVES³

During the war years very few American reports have appeared on the frequency and clinical aspects of pleural effusion. Thus far no investigation of pleurisy has been made in the Army. Ameuille (quoted by Wilson (1)) in 1917 reported that tuberculosis of the serous cavities and especially of the pleura was strikingly frequent in soldiers of the French Army; involvement of the serous membranes occurred in 270 cases in a series of 2,600 tuberculous soldiers.

Ours is a study of 215 cases of tuberculous pleurisy with effusion. Cases of pleurisy secondary to therapeutic or spontaneous pneumothorax are not included in this report; nor are cases which showed only apical pleural thickening or blunting of the costophrenic sinus without evidence of recent active pleurisy. This is necessarily a selected group, since it consists only of male American soldiers hospitalized at Bruns General Hospital, Santa Fe, New Mexico, one of the Army Tuberculosis Centers. The great majority of these soldiers were transferred from other Army hospitals rather than admitted directly. Cases hospitalized on other services are not included in this report. The management of these cases before their arrival at this hospital necessarily varied considerably due to the urgency of the situation in the various theatres of operation, the attitudes of the many different medical officers handling the patients and the very inadequate care and observation given the prisoners of war. To standardize the management of these cases, a Medical Technical Bulletin (TB. MED. 71) was issued in July, 1944 which emphasized the probable tuberculous origin of any "idiopathic" effusion in a young adult and the need for adequate diagnostic procedures and prompt treatment.

Of the 215 cases analyzed, 168 (78 per cent) were white and 47 (22 per cent) were non-white. This latter group was composed chiefly of Negroes, but also included a small number of Indians, Filipinos, Chinese and Japanese. In 114 patients (53 per cent) the effusions were on the right side and in 85 (40 per cent) on the left; 16 (7 per cent) had bilateral effusions.

The past histories revealed that 12 per cent had close contact with an open case of tuberculosis during civilian life. In addition, 11 per cent were liberated prisoners of war, most of whom were exposed to cases of tuberculosis, giving a combined contact history of 23 per cent. Schuman (2) in his series gives the incidence as 20 per cent and Bonilla (3) found that 33 per cent gave a history of contact.

¹ From the Medical Service, Bruns General Hospital, Santa Fe, New Mexico.

² Captain, M. C., A.U.S. Present address: 1150 Grand Concourse, Bronx, New York.

³ Captain, M. C., A.U.S.

The induction miniature X-ray films were available in 88 cases. Of these, 4 revealed probably active tuberculosis and 9 probably inactive disease.

The cases of tuberculous effusion were divided into two groups: (1) definitely tuberculous—the criterion for inclusion in this group was either the isolation of tubercle bacilli from the chest fluid, sputum or other body secretion, or the demonstration of tuberculosis by biopsy or autopsy; (2) probably tuberculous—the cases in this group lacked the above criterion, had no other demonstrable etiology and had positive or unreported Mantoux tests.

Mantoux tests were performed in 150 cases, of which 119 (79 per cent) were positive to first strength PPD; the remainder were found positive to second strength PPD. None of the cases showed exacerbation of the pleurisy following skin testing. Coccidioidin (1:100) skin tests were performed on 105 cases and 8 were positive.

SYMPTOMS

In each case the predominant symptoms were tabulated. Pain (81 per cent) and fever (73 per cent) were outstanding. Cough (39 per cent), fatigue or malaise (28 per cent), dyspnea (25 per cent) and weight loss (23 per cent) were other common symptoms. Hemoptysis occurred in 7 per cent, which is comparable to Erwin's (4) finding of 6 per cent in patients of all age groups and both sexes. Seven cases were discovered to have pleurisy by routine X-ray examination following their admission for other complaints, showing that pleurisy may occasionally have an insidious onset. In one case a routine X-ray film prior to shock therapy for schizophrenia at a neuropsychiatric center showed blunting of the left costophrenic sinus and it was assumed that the pleurisy was inactive. During the treatment the patient ran a low grade fever. Five months later another X-ray film was taken before discharge and this showed a marked increase in the extent of the pleural effusion, which now extended up to the fifth anterior rib.

Another case had a shrapnel wound of the chest. A thoracotomy was performed to evacuate large blood clots; a biopsy showed unsuspected active tuberculosis of the pleura.

The initial symptomatology was occasionally referred to the gastro-intestinal tract rather than to the chest, and the patients complained only of fever, nausea, vomiting and upper abdominal pain. A mistaken diagnosis of intraabdominal disease was frequently made and corrected only following a chest X-ray examination. Some patients, who later developed an effusion, complained of severe chest pain but presented no physical or roentgenological evidence of pleurisy at the first examination. Therefore, we suggest that all patients with unexplained pleuritic pain have follow-up examinations.

EFFUSION

The cases were divided into three groups according to the amount of fluid shown on X-ray films: (a) minimal, fluid obscuring the costophrenic sinus,

28 (12 per cent); (b) moderate, fluid more than minimal but below the fourth anterior rib, 114 (49 per cent); (c) severe, fluid above the fourth anterior rib, 89 (39 per cent). Data on the fluid obtained by aspiration were available in 126 cases. The results of the examinations showed clear amber fluid in 98 (78 per cent), cloudy amber fluid in 14 (11 per cent), bloody fluid in 8 (6 per cent) and purulent fluid in 6 (5 per cent). Cell counts were done in 72 cases, of which 42 (59 per cent) had over 1,000 white blood cells per cmm. and lymphocytes predominated in 56 (78 per cent).

Bacteriological examination of the chest fluid was not available in all cases. The examinations were performed at many different Army installations varying from small station or field hospitals to large chest centers. The examination for acid-fast bacilli by concentration and direct smear in 71 cases was positive in only 6 cases. Out of 50 cultures for tubercle bacilli, 10 were positive; 32 guinea pigs were inoculated and 17 were positive (53 per cent). This is somewhat higher than Farber (5) found in a series of 66 cases of which 19 were positive. It is also slightly higher than the 43 per cent of the 136 guinea pigs inoculated and reported by Kullner (6).

OCCURRENCE OF PARENCHYMAL DISEASE AND DISSEMINATION

In this series we found parenchymal disease in 89 out of 215 cases (42 per cent). Bonilla (3) found 57 per cent in 70 cases, whereas Erwin (4) reported only 7 per cent in 100 cases. This apparent discrepancy between these two investigations may be due to the fact that Bonilla's series was composed of over 70 per cent Negroes. This explanation is borne out by our group in which the non-white patients had a somewhat higher incidence of parenchymal disease (49 per cent in the non-white compared to 39 per cent in the white group, which is suggestive, but the group is too small for the difference to be statistically significant). Non-white patients more often had moderately or far advanced disease than the whites. This is illustrated in the following tabulation:

<i>Cases with parenchymal disease</i>	<i>White</i>	<i>Non-white</i>	<i>Total</i>
Minimal.....	26	7	33
Moderately advanced.....	25	7	32
Far advanced.....	15	9	24
	—	—	—
	66	23	89
	(39% of all white pa- tients)	(49% of all non- white patients)	(42% of all patients)
Frequency of dissemination	20	14	34
	(12%)	(30%)	(16%)

Dissemination, as seen in the above tabulation, occurred in 16 per cent of the cases during the period of observation of six months to one year. All cases were treated with bed-rest after arriving at Bruns General Hospital, although

* Total of 231 effusions, with the 16 bilateral effusions tabulated twice.

their previous treatment had been of different types. Aspiration was performed during the acute phase for diagnosis or to relieve dyspnea. Closed technique without air replacement was preferred. After the acute phase had subsided, aspiration was performed more often to facilitate reexpansion and recovery of pulmonary function. The frequency of dissemination in the non-white group was 30 per cent, compared to 12 per cent in the whites. As expected, the most common sites of dissemination were the lymph nodes, peritoneum, bone and genito-urinary system. There were only 2 cases of miliary dissemination to the lung, one of which also had extrapulmonary miliary spread, as shown at autopsy. Five patients died, and all had widely disseminated disease at autopsy.

BILATERAL EFFUSIONS

Many authors (7, 8, 9) have emphasized the rarity of bilateral effusion. Bird (10) reports a much higher incidence (7 in 48 cases) and Erwin (4) reports 13 per cent. In the present group, 16 (7.5 per cent) had bilateral pleural effusions. Ten of these cases (63 per cent) had parenchymal disease, compared with 40 per cent among patients with unilateral effusions. However, in 6 of these 10 patients the parenchymal disease was minimal in extent. This is in contrast to Wilson (1) who reported that most of his 14 cases of bilateral pleurisy "developed pleuritis as a complication of extensive pulmonary tuberculosis and by direct extension from underlying disease to the pleura."

Fernandes (8) believes that bilateral pleural effusion is a manifestation of miliary tuberculosis and that the collapse produced by the effusion retards the roentgenological appearance of the miliary disseminations. Five of his 6 cases developed miliary spreads in the lungs in a period ranging from one to seven months. In our series of bilateral effusions, all observed more than six months, there was not a single case of miliary tuberculosis. Bilateral pleural effusion may be a manifestation of hematogenous seeding of the pleura, but it is not necessarily a part of an occult miliary tuberculosis.

NONTUBERCULOUS EFFUSIONS

During the period our 215 cases were admitted to the tuberculosis service in this Hospital we observed cases of pleurisy due to infarct, amebic hepatitis associated with right-sided effusion, pneumonia (both bacterial and atypical), coccidioidomycosis, chylothorax and 2 cases of idiopathic pleurisy with tuberculin anergy to second strength PPD.

COMMENT

Erwin (4), in 1944, postulated an interesting pathogenesis of pleural effusion. He suggested that many pleural effusions result from the rupture of a caseous tuberculous hilar node into the pleural cavity, either directly or through a small zone of intervening lung, consolidated by periadenitis. However, he admits that this generally occurs only among children and adolescents. In our group of cases we found hilar adenopathy in only 2 patients, both Negroes; but it should be remembered that all our patients were adults.

Although 89 (42 per cent) of our patients had parenchymal disease, in about three-fourths of these cases the pleurisy and the parenchymal disease were discovered simultaneously, so that it was impossible to state which occurred first. Because of this, we could not arrive at any conclusions as to the incidence of pulmonary tuberculosis following pleural effusion. In addition, our observation period was too short, since many authors have pointed out that pulmonary tuberculosis occurs, in many cases, up to at least five years following the effusion, and in some cases even longer (6).

It is interesting that the non-whites in our series had more frequently parenchymal disease and dissemination than the whites, even though all the patients had been in the service for an average period of more than two years. During this time they had the same quarters and food as the white soldiers and also had identical medical care, so apparently these differences cannot wholly be ascribed to their economic status.

SUMMARY

A total of 215 cases of tuberculous pleurisy with effusion are analyzed; 16 of these had fluid bilaterally.

Roentgenograms taken at induction were available in 88 patients, and 4 (5 per cent) of these showed evidence of probably active disease.

In 50 cases (23 per cent) a history of close contact with cases of active tuberculosis was recorded.

In 89 (42 per cent) parenchymal disease, with a somewhat higher incidence among the non-white group, was present.

The characteristic symptoms were tabulated as well as the gross and bacteriological examinations of the chest fluid.

During the six to twelve-month period of observation, 34 (16 per cent) developed dissemination.

SUMARIO

Pleuresia Tuberculosa con Derrame

En total analízanse 215 casos de pleuresía tuberculosa con derrame, en 16 de ellos bilateral.

Para 88 enfermos había radiografías tomadas a la entrada al Ejército, y 4 (5 por ciento) de ellas mostraban signos de probable enfermedad activa.

En 50 casos (23 por ciento) había antecedentes de contacto íntimo con casos de tuberculosis activa.

En 89 (42 por ciento) existía enfermedad parenquimática, que alcanzaba una frecuencia algo mayor entre los que no eran blancos.

Se tabulan los síntomas característicos así como el resultado de los exámenes macroscópicos y bacteriológicos del líquido torácico.

Durante el período de observación que duró seis a doce meses, 34 (16 por ciento) mostraron difusión.

TUBERCULOUS PLEURISY

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CHRONIC EMPYEMA

Irrigation Treatment with Glycerite of Hydrogen Peroxide Solution A Preliminary Report

WILLIAM B. O'BRIEN,¹ ETHAN ALLAN BROWN² AND HARRY PEARSE³

It has long been recognized that the chief objective in the medical treatment of chronic empyema is the sterilization of the empyema cavity. When, by whatever means, such sterilization has been accomplished, obliteration is successful, convalescence is shortened and Mason's (9) other criteria, the possibility of cure and its corollary, the reduction of mortality naturally follow.

The types of irrigation treatment at present in use are not many, and the results achieved merit brief review.

Ornstein and Herman (13), corroborating and advancing the work of Petroff (14), use a solution consisting of a mercurial solution combined with a sodium tetradecyl sulfate. After the first seven days, irrigations are continued twice weekly. In 98 patients, studied for periods of nine to sixty months, there was complete recovery in 48 patients and full recovery was anticipated in a majority of 28 more patients in process of treatment.

In a discussion of the surgical treatment of empyema by Grow (7), it is stressed by Joannides that almost 90 per cent of his acutely affected patients had recovered following daily irrigation of the cavity with azochloramid (1:3,000) and penicillin (2,000 to 4,000 units) injected intrapleurally. In the 10 per cent of the patients who did not respond, the cavity was opened and treated with azochloramid irrigations three times daily.

Finland (6) reports that more than half of 250 patients with empyema, due to pneumococcus, hemolytic streptococcus and staphylococcus, have been completely cured by aspiration followed by instillation of penicillin. The dosage employed is 50,000 to 200,000 units every twelve to twenty-four hours, the interval between treatments being lengthened in accordance with the amount and character of the aspirated fluid. Concomitant intramuscular injections of penicillin are necessary. Roberts (15) and his colleagues, however, feel that, although penicillin used intrapleurally causes rapid sterilization, it also results in so much pleural thickening that surgical interference is necessary.

Klassen, Miller and Curtis (8), reporting on the treatment of 61 patients studied for a period of ninety months, using merthiolate, azochloramid or dye irrigation, found no more apparent benefits than that following the use of saline. In 1942, these workers began using sodium sulfathiazole (5 per cent solution) with disappearance of streptococci and staphylococci, but naturally with no effect upon the tubercle bacilli. In their experience, aspiration and irrigation alone have been of no apparent value in the treatment of empyemata.

¹ Senior Physician, State Sanatorium, Wallum Lake, Rhode Island Department of Health.

² Physician-in-Chief, Allergy Section, The Boston Dispensary, Boston, Massachusetts.

³ Laboratory Director, State Sanatorium, Wallum Lake, Rhode Island Department of Health.

Donaldson and Samuel (5) report that with aspiration, lavage with distilled water and instillation of tyrothricin (10 to 50 mg.) there were no effects upon the character or the amount of purulent exudate in 8 patients suffering from tuberculous empyemata.

That peroxides have their place in the treatment of empyema is shown by the recent report of Strieder and Lynch (16) who describe the treatment with zinc peroxide of 90 patients presenting putrid empyemata caused by anaerobic organisms acting symbiotically. For immediate postoperative treatment, a gauze pack saturated with activated zinc peroxide is placed partly in the wound and partly in the pleural cavity. It is reported as deodorizing the wound as well as producing clean granulation tissue.

The present paper is concerned with the results following the irrigation of empyema cavities with a new bacteriotoxic solution, glycerite of hydrogen peroxide. A secondary stabilizing agent, 8-hydroxyquinoline, is present in an amount of 0.1 per cent. Since the data concerning its preparation, properties and mode of action are in the process of publication, these require brief discussion.

Ever since its discovery by Thénard, in 1818, hydrogen peroxide has been known to possess detergent, deodorant and hemostatic properties. Less often emphasized are its other positive virtues, in that it is, by its very composition, nontoxic and nonallergenic and, in addition, nonirritating in effectively bactericidal concentration. It is also a naturally occurring end-product of bacterial metabolism (10).

On the other hand, the aqueous solutions are relatively unstable and in the presence of blood decompose so rapidly that the bacteria present are rarely, if ever, affected. In the absence of blood, peroxides act slowly with the result that they are classified as having low phenol coefficients, a false criterion for nonphenolic types of antiseptic solutions and especially for those which are used for the treatment of chronic conditions, such as infections of the ear, skin and lungs and empyemata.

It occurred to one of us (E.A.B.) and his collaborators that, since the aqueous solutions were so unstable and their effectiveness on wound surfaces was so transient, a water-free peroxide added to a water-free solvent would both enhance the positive virtues of peroxide solutions and overcome some of their disadvantageous qualities. At the time our work was initiated, pure (100 per cent) hydrogen peroxide, relatively water-free, was not available. Urea peroxide crystals (4 per cent) were used as a means of introducing hydrogen peroxide (1.5 per cent) into anhydrous glycerol. Although the glycerol is more stable than is the aqueous solutions, the catalytic effects of metallic impurities contained in the glycerol had to be neutralized. Oxine (8-hydroxyquinoline), itself a bacteriostatic agent (12) because it reacts with metals to form salts incapable of being used by microorganisms (18), was added to the solution and, since it reacted with metallic impurities in the glycerol, prevented catalysis of the peroxide.

The solution possesses the following dynamic effects. The glycerol is viscous and hygroscopic, remaining *in situ* and washing plasma to the surface of dam-

TABLE 1

The effects of glycerite of hydrogen peroxide upon the types of bacteria in 9 patients with empyema

PATIENT	STAPHYLOCOCCUS AUREUS	β -HEMOLYTIC STREPTOCOCCUS	PROTEUS VULGARIS	PSEUDOMONAS PYOCYANEUS	DIPHTHEROID BACILLUS	PRESENT CONDITION OF PATIENT
E.R.B.	Cultures sterile in twelve weeks	Cultures sterile in twelve weeks				Cultures sterile. Sinus open with slight drainage.
F.M.A.	Cultures constantly positive		Cultures constantly positive			Prognosis of patient hopeless. Diagnosis: Progressive tuberculosis and diabetes mellitus.
M.C.	Cultures sterile in four weeks		Positive on one occasion only	Cultures constantly positive	Positive on one occasion only	Sinus completely closed. Patient discharged well.
H.F.D.					Cultures sterile in one week	Sinus completely closed. Patient discharged, working at Sanatorium.
J.E.R.	Cultures sterile in fourteen weeks					Cultures sterile. Sinus reduced in size.
Y.M.M.	Cultures sterile in eight weeks			Cultures constantly positive	Cultures positive after two months	Thoracoplasty wound decreased in size and externally clean. Discharge reduced in amount.
E.G.D.	Cultures sterile in five weeks					Died of acute myocardial failure.

TABLE 1—*Concluded*

PATIENT	STAPHYLOCOCCUS AUREUS	B-HAEMOLYTIC STREPTOCOCCUS	PROTEUS VULGARIS	PSEUDOMONAS PYOCANEUS	DIPHTHEROID BACILLUS	PRESENT CONDITION OF PATIENT
J.J.E.	Cultures sterile in ten weeks					Cultures ster- ile. Cav- ernostomy opening partly epi- thelialized.
J.E.C.	Positive on one occa- sion only	Cultures sterile in one week		First posi- tive nine months after treat- ment	Positive on one occa- sion only	Sinus reduced in size. Closure of empyema space in pro- cess by tho- racoplasty.

aged tissue. Its surface tension keeps the oxygen released by peroxidase systems within the solution, churning it continuously and thereby renewing the interface between the antiseptic and the infected area. The peroxide action is therefore prolonged.

The hydrogen peroxide is a nonselective bacteriostatic and bactericidal agent. It not only affects the usual Gram-positive and Gram-negative bacteria, but is bactericidal for *M. tuberculosis* (*var. hominis*) by laboratory and clinical tests (4). The urea which remains is bacteriostatic (17) and also is peptizing, promoting wound healing (11).

Tissue tolerance studies (1) have shown the solution to be nonirritating, both by patch tests upon normal persons, and by prolonged application to infected skin and mucous membranes in over 800 patients. The results of treating mixed infections of the middle ear have been reported (3); 17 patients cleared completely in fourteen days and the remaining 12 in thirty-eight days.

The present paper is concerned with the use of the solution in mixed tuberculous empyemata. Although the series, which consists of 9 patients, is small, the results were considered worthy of a preliminary report.

Eight of the patients presented empyemata, complicated by pleurocutaneous fistulae and the ninth, a secondarily infected tuberculous cavity with surgical cavernostomy. In 4 patients there was clinical evidence of broncho-pleural fistulae. In no case did we attempt to differentiate between primary pyogenic infection and pyogenic infection as a secondary complication of a tuberculous lesion, although in 7 patients there was a tuberculous infection as confirmed by guinea pig inoculation.

Since in 3 patients the draining sinuses were present upon admission, and a fourth was proved after surgical drainage of the empyema, the duration of infection, exact or average, is difficult to ascertain. The bacterial studies confirmed that it was longer than six months before treatment was initiated.

Table 1 illustrates the type of bacterial infections treated and the conclusions drawn from laboratory data. The *Staphylococcus aureus*, which was present in 8 patients, disappeared in four to fourteen weeks. The beta-hemolytic streptococci, found twice, were absent after four weeks. *Proteus vulgaris* was present once in the only patient in whom the staphylococci were not eliminated. *Pseudomonas pyocyaneus* was found 3 times and diphtheroids, 4 times. This latter microorganism was present on one occasion in each of 2 patients and disappeared in one week in the third, remaining for two months in the fourth.

The medical treatment consisted of the instillation, twice daily, of 3 cc. of the glycerite of hydrogen peroxide solution (1.5 per cent) through the cutaneous opening, which was immediately closed with a firm sterile plug.

CASE REPORTS

The protocols briefly describe the clinical course of each patient.

1: E.R.B. Female, age 42, readmission in October, 1944 for the closure of a fistula in a bronchial stump. Cultures of the material and the draining pleuro-cutaneous fistula demonstrated *Staphylococcus aureus* and hemolytic streptococci. In January, 1945, treatment with the glycerol peroxide solution was started. The beta-hemolytic streptococci disappeared in four weeks and the *Staphylococcus aureus* in twelve weeks. The cultures have consistently been negative for bacteria, the most recent studies having been done in November, 1945 and in February, 1946. The sinus is gradually being reduced in size, although still open.

2: F.M.A. Male, age 29, admitted in 1940 for severe diabetes and advanced bilateral pulmonary tuberculosis. In 1941, a left pneumothorax followed by pneumonolysis on two occasions was performed. The adhesions were not amenable to cauterization. A left phrenic crush was done in August, 1942. In September, 1943, a staphylococcus empyema on the left side was treated by rib resection and drainage. All antiseptic solutions, including sulfathiazole and penicillin, had no effect upon the heavy growth of *Staphylococcus aureus*. The use of glycerite of hydrogen peroxide, in December, 1944, had some possible slight effect upon the bacteria. At no time were cultures negative. The patient's prognosis is extremely poor.

3: M.C. Female, age 37. Bronchoscopy and biopsy in 1944 demonstrated an epidermoid carcinoma. A right total pneumonectomy was performed in October, 1944 by Dr. Richard B. Overholt. A right pleural empyema was treated with penicillin with temporary success. Continued hyperpyrexia suggested a recurrence and aspiration demonstrated *Pseudomonas pyocyaneus*, necessitating rib resection and drainage. This was followed by a complete right thoracoplasty in January, 1945. Penicillin had no effect upon the organism. Following irrigation with glycerite of hydrogen peroxide, there was a gradual diminution in bacterial growth and eventual complete obliteration of the empyema cavity. The cultures were positive on one occasion only for *Proteus vulgaris* and diphtheroids. No staphylococci were found after four weeks. Cultures were constantly positive for *Pseudomonas pyocyaneus*. The patient has been discharged to her home.

4: H.F.D. Female, age 30. Readmitted with a left broncho-pleural fistula, for which tube drainage of the left pleural space was instituted in July, 1942. The patient's progress

was poor until March, 1943, when she made so marked an improvement that in October, 1943, a left thoracoplasty was recommended and performed in four stages. The residual empyema was treated with various antiseptic solutions, including sulfathiazole and penicillin, with occasional sterile cultures, the chief organism consistently present being a diphtheroid. Guinea pig inoculation for tuberculosis was positive. In December, 1944, the glycerol peroxide solution was used as above with immediate and consistent sterilization of the cavity, which healed rapidly within a period of four weeks. The patient is still well (February, 1947) and working as an attendant at the Sanatorium.

5: J.E.R. Male, age 66. Admitted with empyema and left broncho-pleural fistula, for which rib resection and drainage was carried out in April, 1943, followed by thoracoplasty in several stages. The chief organism was at first a nonhemolytic streptococcus, which was replaced by a *Staphylococcus aureus* and later a concomitant diphtheroid bacillus. Treatment with glycerol peroxide solution was applied in January, 1945, and cultures became sterile after fourteen weeks, remaining sterile until the patient's discharge in August, 1945. The sinus is almost completely closed, the patient receiving treatment at the Out-Patient Department of the Rhode Island Hospital.

6: Y.M.M. Male, age 51. The patient entered the Sanatorium with a mixed empyema of the left side of nine months' duration. The presence of tuberculosis was confirmed histologically. The empyema was drained and treated three months later with multiple-stage thoracoplasty. At the time of admission, the thoracoplasty wound was wide open, heavily infected, with profuse drainage. The patient was critically ill. The cultures and direct smears showed tubercle bacilli in addition to *Staphylococcus aureus* and *Pseudomonas pyocyaneus*. The glycerol peroxide treatment was initiated in August, 1945. The staphylococci disappeared in eight weeks. The cultures in October and November, 1945 and February, 1946 show a rare pyocyaneus colony and a rare diphtheroid. No tubercle bacilli were found. The wound is clean, diminishing in size and draining slightly. Additional thoracoplasty will probably be necessary to close the empyema space.

7: E.G.D. Male, age 26. Admitted critically ill with a right mixed empyema and broncho-pleural fistula, for which rib resection and drainage was performed in September, 1943. With the patient's clinical improvement, multiple-stage thoracoplasty was done. Profuse drainage persisted, the cultures demonstrating a *Staphylococcus aureus*, which was resistant to penicillin. The glycerol peroxide treatment was initiated in December, 1944, the cultures becoming sterile in five weeks and remaining sterile for three months, during which time the sinus tract showed diminution in size and drainage. In July, 1945, the patient died in an attack of acute myocardial failure. Permission for postmortem studies was refused.

8: J.J.E. Male, age 46. Admitted with bilateral advanced tuberculosis with cavitation of the right upper lobe. A right pneumothorax was begun in February, 1942. Collapse was unsatisfactory and the pneumothorax was discontinued. The disease in the left lung increased and a left pneumothorax was induced, followed by a two-stage thoracoplasty in May and June, 1943. Continued advance of the tuberculous infection accompanied by dyspnea and severe pain necessitated an intercostal neurectomy, followed by a right cavernostomy and drainage tube. The culture showed hemolytic and nonhemolytic *Staphylococcus aureus* and tubercle bacilli. The infection was resistant to both sulfathiazole and penicillin. The glycerol peroxide treatment was initiated in December, 1944

with sterile cultures apparent in ten weeks and interim cultures up to and including February, 1946, demonstrating continued sterility. The wound is open, clean and shows epithelialization.

9: J.E.C. Male, age 33. A broncho-pleural fistula had developed in August, 1944. A rib resection and drainage was performed in September, 1944. Guinea pig inoculation revealed tubercle bacilli. Cultures proved *Staphylococcus aureus* and beta-hemolytic streptococci initially, with *Pseudomonas pyocyaneus* occurring nine months later. Diptheroid bacilli were present on one occasion. Glycerol peroxide irrigation was started in January, 1945, with sterilization of the cavity in four weeks. Infection, as demonstrated by a slight growth in culture material, has returned on several occasions. The patient is undergoing multiple-stage thoracoplasty and a small empyema space is still under treatment with the solution.

SUMMARY

Glycerite of hydrogen peroxide (1.5 per cent) derived from urea peroxide (4 per cent) stabilized with 8-hydroxyquinoline (0.1 per cent) applied by simple instillation, 3 cc. twice daily, has been effective in the sterilization of empyema cavities in 7 of 9 patients with cutaneous fistulae. Laboratory studies proved these to be infected with *Staphylococcus aureus* and beta-hemolytic streptococci resistant to sulfathiazole and penicillin.

The solution reduced the amount of growth of *Pseudomonas pyocyaneus*. The presence of the tubercle bacillus did not hinder the effect of the solution upon the control of the secondary invading microorganisms.

The patients are still under observation and will be reported upon in a second series, comprising a larger group of subjects.

SUMARIO

Empiema Crónico: Lavado Terapéutico con Solución de Glicerito de Peróxido de Hidrógeno

El glicerito de peróxido de hidrógeno (1.5 por ciento) derivado del peróxido de urea (4 por ciento), estabilizado con 8-hidroxiquinolina (0.1 por ciento), aplicado por instilación simple, 3 c.c. dos veces diarias, resultó eficaz para esterilizar cavidades empiemáticas en 7 de 9 enfermos que tenían fistulas cutáneas. Los estudios de laboratorio demostraron que éstas se hallaban infectadas con *Staphylococcus aureus* y estreptococos hemolíticos beta resistentes al sulfatiazol y la penicilina.

La solución hizo bajar el número de colonias de *Pseudomonas pyocyaneus*. La presencia del bacilo tuberculoso no impidió el efecto de la solución sobre los microbios invasores secundarios.

Los enfermos se hallan todavía en observación y se describirán en la segunda serie, que comprende un número mayor de casos.

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NONREACTORS TO TUBERCULIN^{1,2}

An Analysis in a Large Sanatorium

M. R. LICHTENSTEIN

Tuberculin tests are used for three purposes: first, in surveys to pick out reactors for X-ray examination; second, to determine the tuberculosis infection rate in various places; and third, as an aid in excluding the diagnosis of tuberculosis in the individual patient. This paper is concerned only with the use of tuberculin as an exclusion test at the Municipal Tuberculosis Sanatorium of Chicago, with an analysis of the results over a period of fourteen years.

Previous work using the method of P. D'Arcy Hart (1) has been reported from the Municipal Tuberculosis Sanatorium (2) in 1932, and by Musacchio from Detroit (3) in 1940. These studies have verified Hart's conclusion that practically all patients with tuberculosis react to tuberculin. The small percentage of known tuberculous nonreactors consists mainly of those who are very cachectic, senile or have miliary tuberculosis.

Nonreactors with proved pulmonary tuberculosis who do not fall in the above groups have occasionally been reported, but the work usually has been open to the criticism that the testing was incomplete and that the materials were not standardized. This study was directed particularly at the analysis of the non-reactor group, in an attempt to clarify the exact meaning of such a finding.

METHOD

Old Tuberculin was used. It was standardized, at intervals, by comparison with PPD on the opposite arms of a series of patients. The intracutaneous test was done by the method of P. D'Arcy Hart, using dilutions of 1:10,000, 1:1,000, 1:100 and 1:10 serially at forty-eight-hour intervals, until a reaction was obtained or all dilutions were used.

The diameter of the indurated area was recorded. Tests were begun within the first three days following admission.

Over the fourteen-year period from 1932 to 1946, a total of 15,976 adults were admitted to the Municipal Tuberculosis Sanatorium. Of these, 11,749 were tuberculin-tested on admission. Those not tested were the moribund patients and, from 1942 to 1946, those who had known positive sputa prior to admission.

RESULTS

Of the 11,749 patients tested, those who were reactors and those nonreactors who were very ill or senile (over 70 years) are excluded from further consideration. The term "very ill" was arbitrarily used for those unable to walk. This left 142 patients, or 1.2 per cent, who were completely insensitive, meaning that they failed to react to a 1:10 dilution intracutaneously. Every effort was made to arrive at an accurate final diagnosis in this group, by using all the available

¹ From the City of Chicago Municipal Tuberculosis Sanatorium, North Pulaski Road and Bryn Mawr Ave., Chicago 30, Illinois.

² Read, in brief, before the Mississippi Valley Trudeau Society, September, 1946.

clinical, X-ray and laboratory resources of the institution. Follow-up observations were made in many of these patients for several years after discharge.

The final diagnoses in the 142 nonreactors are listed in table 1. The group of patients listed as "no disease or undiagnosed" consisted mainly of patients whose disease had subsided by the time they were admitted, so that accurate diagnosis was impossible. Most of them had probably nontuberculous respiratory infections.

The last 4 patients listed in table 1 constitute exceptions to the general rule that all tuberculous patients react by the method used. A positive sputum was never obtained from any of the 4 during residence in the Sanitarium. In 3,

TABLE 1
Final diagnoses in 142 nonreactors to tuberculin

A. Nontuberculous	
(1) Infection, respiratory.....	56
(2) Infection, extrapulmonary.....	12
(3) Tumors.....	7
(4) Hodgkins disease.....	3
(5) Cardiac diseases.....	9
(6) Blood dyscrasias.....	2
(7) Malnutrition.....	7
(8) Neuroses.....	4
(9) Asthma.....	2
(10) Spontaneous pneumothorax.....	4
(11) Sarcoidosis.....	12
(12) No disease or undiagnosed.....	20
B. Tuberculosis, pulmonary.....	
	4

tubercle bacilli were found in gastric lavages and one also had a positive sputum culture. Two of these patients died about two years after discharge of chronic progressive pulmonary disease. The other 2 are apparently well up to the present time.

CASE REPORTS

A brief outline of the significant facts in the case histories of the 4 tuberculous nonreactors follows:

Case 1: M. G., a 24-year-old married woman of Italian descent, had a miscarriage following an accident in 1935. Metrorrhagia occurred for six weeks until surgical interference. She never felt well after this, complaining of weakness and loss of weight. In February, 1938 she had scarlet fever, and an X-ray film revealed a pleural effusion and apical disease. Admitted to the Municipal Tuberculosis Sanitarium in July, 1938, X-ray examination revealed bilateral apical infiltrations and fibrosis. Tuberculin tests were completely negative. She was ambulatory, fever-free and weighed 98 pounds. During two years in the Sanitarium she gained 4 pounds and improved in strength. During this period, tubercle bacilli were found only on guinea pig inoculation of sputum and stomach lavages on two occasions. Tuberculin tests, in all dilutions, were repeatedly negative during

her stay. After her discharge in May, 1940, she remained in fairly good health for about one year; then progressive pulmonary disease caused her death at Cook County Hospital in December, 1941.

Case 2: L. M., a 40-year-old married woman, had a history of hemoptysis in 1921 (2 cupfuls), repeated in 1928 and 1932. Right pneumothorax was given in 1932 and was maintained until 1937. Hemoptyses recurred in 1937. She was admitted to the Municipal Tuberculosis Sanitarium on February 10, 1938, complaining of cough, expectoration, loss of weight and weakness. X-ray films revealed bilateral apical fibrosis and scattered, multiple calcifications. Although positive sputum had been found repeatedly prior to 1936, during her two-month stay in the Municipal Tuberculosis Sanitarium sputa were negative. However, acid-fast bacilli were found in a proctoscopic smear. Tuberculin tests were negative in all dilutions. The patient was ambulatory and fever-free. Her condition remained about the same until October, 1939, when she left Chicago.

Case 3: C. N., an 18-year-old married woman, had a history of exposure to her tuberculous mother up to the age of 4. She was clinically well till July, 1936. In December, 1936, she was admitted to the Municipal Tuberculosis Sanitarium, complaining of cough, expectoration and loss of weight. She was ambulatory and fever-free. Tuberculin tests were negative in all dilutions. X-ray examination revealed bilateral apical fibrosis with small cavities. Sputa were always negative, but one stomach lavage was positive on culture and guinea pig inoculation. Bilateral pneumothorax was given. She was kept under observation until June, 1938. Repeated tuberculin tests were negative, until the end of this period, when she reacted to a 1:1,000 dilution. She became worse after this and died of progressive pulmonary disease in September, 1939.

Case 4: J. J., a 30-year-old married man, had a history of pneumonia (?) in 1932 causing him to be kept on bed-rest for one year. He was well after this till May, 1942 when pain in his right knee began. In January, 1943, chills and fever occurred and a diagnosis of undulant fever was verified at two hospitals. In April, 1943, tubercle bacilli were found in a sputum specimen at one of these hospitals. The patient was admitted to the Municipal Tuberculosis Sanitarium in May, 1943. X-ray films revealed an area of infiltration in the right mid-field. He had been having fever up to 104.0° F. for some time. Tuberculin tests were negative in all dilutions on admission, but became positive to 1:100 in September, 1943. He improved, was discharged in July, 1944 and has remained well up to the present. During his stay a sputum culture and guinea pig inoculation were positive for tubercle bacilli.

In attempting to explain the tuberculin anergy of these 4 tuberculous patients, it is evident that no obvious reason can be assigned. It is notable, however, that one patient was known to have tuberculosis over a period of many years; another was kept in bed one year for "pneumonia" ten years before admission; and the other 2 had fibrotic lesions when first seen. This suggests that the common basis for anergy in these patients may have been the long duration of the tuberculous disease prior to our tests. We have previously demonstrated (2) that tuberculin allergy becomes depressed as the duration of disease increases. In one case the presence of high fever with brucellosis may well have contributed to the patient's anergy. In view of these cases, it appears that long duration of pulmonary tuberculosis may occasionally be a cause for tuberculin anergy.

DISCUSSION

The accumulated data over these fourteen years indicate that about 98 per cent of admissions are tuberculin reactors. Most of these are patients with tuberculosis, a few are nontuberculous.

The remaining 2 per cent consists of nonreactors. Many of these are moribund or senile patients with obvious tuberculosis. The remaining nonreactors constitute the group in whom this test is of most value. Of 142 such patients, 138 proved to be nontuberculous. In 4 patients, 3 per cent of the nonreactors, or 0.03 per cent of the total, tuberculosis was present. Thus the finding of complete insensitivity to tuberculin is a highly accurate but not perfect indication that the patient is nontuberculous. Tuberculin anergy is sufficiently reliable that it should be considered a strong warning to isolate and investigate the patient at once.

It is evident that the private practitioner and the general hospital could well use this test before sending patients to sanatoria, to avoid exposure of nonreactors to bacilliferous patients. The test should certainly be done on patients in whom pulmonary disease is found on chest roentgenograms.

Patients entering sanatoria, unless known to have positive sputa, should receive tuberculin tests by an adequate method. The method of Hart is the most thorough. The use of PPD, especially when the second strength dose is repeated, is also adequate. Nonreactors, with the exception of patients who are cachectic or senile, should be presumed to be nontuberculous and isolated until their examination is completed.

The falling infection rate in tuberculosis is making the percentage of nonreactors progressively larger as time goes on, thus making the test more valuable. The wide-spread occurrence of atypical pneumonia and numerous other pulmonary diseases has complicated the problems of diagnosis.

CONCLUSIONS

1. Tuberculin tests were done on 11,749 patients admitted to the Municipal Tuberculosis Sanitarium of Chicago from 1932 to 1946. The method of Hart was used.

2. Omitting cachectic and senile patients, it was found that practically all tuberculous patients were reactors.

3. Only 142 nonreactors were found in the group; 138 of these were found to be nontuberculous. Four patients, or about 3 per cent of the nonreactors, or 0.03 per cent of the total, were found to be tuberculous. In these 4 patients, the long duration of the disease is suggested as a possible explanation for anergy.

4. Tuberculin tests, when performed by an adequate method, constitute a useful means for the presumptive exclusion of the diagnosis of tuberculosis

CONCLUSIONES

Los Negativos a la Tuberculina

1. En 11,749 enfermos recibidos en el Sanatorio Municipal de Chicago de 1932 a 1946 ejecutáronse reacciones a la tuberculina, utilizándose la técnica de Hart.

2. Omitiendo los caquéticos y seniles, prácticamente todos los tuberculosos reaccionaron positivamente.

3. En el grupo sólo se descubrieron 142 que no reaccionaron, y 138 de ellos no resultaron tuberculosos, en tanto que 4, o sea aproximadamente 3 por ciento de los negativos y 0.03 por ciento del total, sí resultaron tuberculosos. En esos 4, la prolongada duración de la enfermedad ofrece una posible explicación de la anergia.

4. Ejecutadas con una técnica adecuada, las reacciones con tuberculina representan un medio útil para la exclusión presuntiva del diagnóstico de tuberculosis.

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TUBERCLE BACILLUS ANTIGENS^{1,2}

Biological Properties of Two Substances Isolated from Paraffin Oil Extract of Dead Tubercle Bacilli

NINE CHOUCROUN

Two fractions of biological significance have been isolated from paraffin oil extract of dead tubercle bacilli:

- 1: An antigen, which seems to be the "hypersensitizing antigen" of the tubercle bacillus.
- 2: A carbohydrate-lipid complex, which has the property of producing lesions in the lung when an amount as small as one gamma is injected intraperitoneally, in paraffin oil. This carbohydrate induces antibody formation when injected into normal animals.

It is a well known fact that heat-killed tubercle bacilli retain many important properties of the living organisms. This was first revealed in the "Koch phenomenon" by the specific response of the infected animals to the cutaneous injection of heat-killed as well as living bacilli. Since then it has been known that animals infected with tubercle bacilli undergo two changes of great significance in the disease tuberculosis: (1) a state of hypersensitivity shown by the specific local and general reaction of the body to the intracutaneous reinjection of living or dead bacilli; (2) a state of acquired resistance revealed by the quick healing of the ulceration formed at the site of inoculation, in contrast to the persistent ulceration formed in animals not previously infected.

When it was established that dead as well as living tubercle bacilli have the power of inducing true tuberculin type hypersensitivity (1) and acquired resistance (2) in experimental animals, it became clear that the bacterial cell, as cultivated *in vitro*, contains among its different constituents—proteins, lipids, carbohydrates—the fractions which must be responsible for these specific effects.

Since, in experimental animals, these specific effects appear together, following infection (or immunization with dead bacilli), it has long been thought that they were both manifestations of a single phenomenon, the state of hypersensitivity being the promotive factor of acquired resistance. The state of hypersensitivity (easy to observe and to follow by the skin tuberculin reaction) was investigated as a factor related to immunity in experiments where the hypersensitivity was induced by whole dead bacilli (3). It was found that the hypersensitized animals were more resistant to subsequent injection of living bacilli than were normal control animals not previously hypersensitized. But the experiments carried out to investigate whether or not the two states of hypersensitivity and acquired resistance closely parallel each other, led to the conclusion that there was no correlation between the intensity of skin sensitization to tuberculin and resistance to infection (4). Dissociation of the phenomena of hypersensitivity to tuberculin and acquired resistance has also been demonstrated by other techniques (Rich (5)).

¹ From the Department of Public Health and Preventive Medicine, Cornell University Medical College, New York, New York.

² This study was carried on under a grant from the Josiah Macy, Jr. Foundation.

It was clear, therefore, that in the body of the killed tubercle bacilli there were two separate antigens which were responsible for the specific effects of hypersensitization and immunity, respectively. The great interest in having these antigens separated one from the other is obvious.

A clear indication was given as to the specific nature of the sensitizing antigen by the fact that only the protein fraction of the bacilli has been found to have the capacity to provoke the typical tuberculin reaction in the hypersensitized animals (6). No such plain indication was given as to the specific nature of the antigen responsible for the development of acquired resistance in experimental animals.

From each of the fundamental constituents of the tubercle bacillus (proteins, lipids, carbohydrates), fractions have been isolated which have the properties of reacting specifically with antibodies formed during infection or immunization with dead bacilli. Among these fractions, protein (7) and lipid (8) components have been found to be actively antigenic in inducing antibody formation when injected into normal animals. But none of these true antigens has been shown to have the immunizing property of promoting the development of acquired resistance (9).

As to the carbohydrate fractions (10), which showed a high degree of reaction with the serum of animals immunized with the tubercle bacillus, none of them had been found to be a complete antigen, that is, to have the capacity of inducing antibody formation when injected into normal animals. The specific nature of the immunizing antigen remained still undefined.

Because of the presumed nature of the sensitizing antigen, much work was undertaken to identify this antigen among the tuberculo-proteins which have been isolated from the tubercle bacillus. But none of these had been shown to have the power of establishing a true tuberculin-type hypersensitivity when injected into normal animals. Even large amounts of extracted tuberculo-protein failed to sensitize the animals either to Old Tuberculin or to the bacillus. Even a combination of all elements (11) extracted from the tubercle bacilli failed to establish the type of hypersensitivity readily established by the injection of either living or dead organisms. All these unsuccessful efforts gave rise to the strong belief that only the whole body of the bacillus, dead or alive, had the capacity to sensitize animals to Old Tuberculin or to the bacillus itself.

The sensitization which develops in animals as a result of immunization by dead bacilli becomes quite comparable to that developed by living organisms when the dead bacilli are injected in *paraffin oil* instead of saline solution. The experiments of Thomson; Hagan and Levine; Opie; Coulaud; Sacnz; and Rist (12) established clearly that the inoculation of a paraffin oil suspension of heat-killed tubercle bacilli produces a state of hypersensitivity at least as intense as that given by living tubercle bacilli (and much more intense and permanent than that given by the same amount of dead bacilli in saline solution). In experiments where the bacilli were suspended in a mixture of oil and saline, the specific hypersensitivity was shown to be proportional to the amount of paraffin oil (13). The oil suspensions of heat-killed tubercle bacilli also produced the

appearance of lesions far from the site of inoculation, whereas suspension in saline gave merely local lesions. Pure paraffin oil alone does not produce these effects.

Furthermore, it was shown (14) that the lesions produced in rabbits by intraperitoneal injection of dead bacilli, human or bovine, in paraffin oil, are comparable to those caused by living human or bovine bacilli (a small effect with human bacilli; a great effect with bovine). This remarkable specific response indicated clearly that the pathogenicity of the bacilli was due to its chemical constitution.

In spite of achieving such results, which approached more and more closely those induced by the living bacilli, workers in the field were still of the opinion that the whole organism was necessary to produce the effect of hypersensitivity and lesions. It was generally thought that the oil, *excipient irresorbable*, was acting only by altering the tissue and making it more vulnerable to the effects of the bacilli.

It occurred to me that the mechanism by which the paraffin oil enhances the effects of dead bacilli could be different and might consist in the removal of substances from the bacilli by the paraffin oil. This assumption proved to be correct.

FIRST INVESTIGATIONS³

Paraffin oil⁴ which had been in contact with dried dead bacilli, human or bovine, was subjected to prolonged centrifugation, in order to separate it from the suspended bacilli.

The first indication that the oil removed substances of biological significance was the fact that it gave specific precipitation when in contact with immune rabbit serum.

To determine whether this oily antigen was of any biological importance, it was injected into guinea pigs and rabbits. After four weeks, the animals were tested for sensitization and antibodies, respectively. It was found that the inoculation of the oil extract stimulated the formation of antibodies in rabbits, and established a definite sensitization to Old Tuberculin in guinea pigs (15).

In order to find the agent responsible for this sensitization, we tried to extract the material from the oil by extraction with the usual organic solvents. After

³ These first investigations were carried on in Paris, France (Institut de Biologie) from March, 1939 until June, 1940, at which time they were interrupted by the war.

We wish to take this opportunity to give full credit to Dr. A. Boquet for his invaluable help at the start of this work, not only in making available to us the resources of his laboratories, but also in supervising each step of our biological investigations; to thank Dr. A. Saenz and Dr. W. Schaeffer for their coöperation; to thank also Dr. A. Baelesse for his gracious help in reading the many X-ray films of the animals, which were taken at the Cancer Institut.

The work was resumed at Cornell University Medical College (Department of Public Health and Preventive Medicine) in the spring of 1942.

⁴ The mineral oil used in France was obtained through distillation of petroleum from Peru; the mineral oil used at Cornell was the "heavy" kind of Eimer and Amend.

many unsuccessful attempts, a precipitate was obtained with the aid of dioxane. This precipitate and the filtrate (freed of dioxane by vacuum at room temperature) were separately injected into guinea pigs intraperitoneally in paraffin oil. Only the precipitate established the state of hypersensitivity in the guinea pigs.

This precipitate was then subjected to extractions with many organic solvents, such as methyl alcohol, chloroform, ether and petroleum-ether. Each extract, separately and in combination with every other one, was then inoculated intraperitoneally, in paraffin oil, into guinea pigs.

Only the residue, alone or mixed with another fraction, was found to sensitize the animals. We temporarily abandoned the study of sensitization in order to follow the new and striking fact that was brought out during the course of the explorative experiments.

Among the fractions obtained from the precipitate *P*, the chloroform extract appeared to be very toxic for the animals (16). Two gamma of this chloroform extracted material, the smallest dose tried, were sufficient to produce lesions in the lungs and usually to kill the animals, when injected intraperitoneally in paraffin oil. At autopsy there were lesions in the lungs very similar to those produced in animals by the injection of whole dead bacilli in paraffin oil. Those animals that did not die within three to four weeks following the injection of this "toxic" material recovered. The progress and regression of the congestion and lesions in the lungs were followed by X-ray examinations at ten-day intervals. More than 100 guinea pigs were viewed, some of them as many as ten times.

Since such an effect was never observed in the controls (either normal controls or those which received pure paraffin oil alone) we thought, at that time, that we were observing a phenomenon of primary toxicity due to the injection of the chloroform extracted material. The same effect was not observed when the same material was injected intraperitoneally in saline or subcutaneously in oil.

As we were not able to duplicate this lethal effect with the homologous chloroform substance extracted in this country, it is probable that the death of the animals (which so constantly occurred in experiments carried out over a period of many months) was a phenomenon of secondary toxicity, possibly due to the physiological state of the particular guinea pigs used. This in itself would be an interesting matter to follow.

The hypothesis that the paraffin oil available in France had a different selective power of extraction from that of the oil used here is not excluded and deserves more investigations which might possibly lead us to identify a principle of primary toxicity in tubercle bacilli. The remarkable fact remains that such a small amount as 2 gamma of this material was able, consistently, to produce macroscopic lesions in the lungs of normal guinea pigs.

In summary, these first investigations showed that paraffin oil removed from tubercle bacilli fractions which have the capacity to produce hypersensitivity and lesions—effects which are precisely those of the bacillus itself, which are enhanced by the paraffin oil.

EXPERIMENTAL

We shall now describe the actual process of extracting these two substances, that is, the hypersensitizing and the "toxic" fractions, in order that each one of them might be as free as possible from the other.

Preparation of the Oil Extract (Chart 1)

The tubercle bacilli (virulent human strain P_{B15}) were grown on Long's synthetic medium in flasks of 1,000 ml. capacity in our laboratory, or in milk bottles at the Wyeth Corporation.⁵ Six to 7-week-old cultures were killed by autoclaving (25 min. 15 lb.).

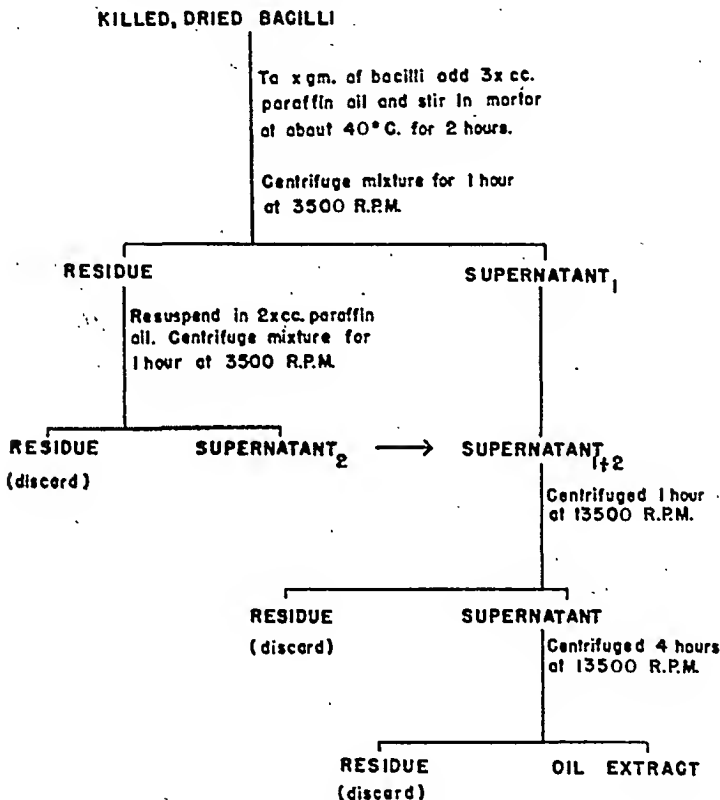


CHART 1. Preparation of the oil extract.

The cultures were filtered over paper (two sheets of E and D filter paper No. 619) and thoroughly washed with distilled water five or six times, until the filtrate was colorless. The paste consisting of bacilli was then taken up from the filter and spread in large petri dishes and put in the incubator at 37°C. to dry. This process was accelerated by manipulating the bacilli every day with a spatula.

When dried, the bacilli were ground in a mortar to reduce the size of the clumps, which were then further ground in a large coffee grinder. The dried powder was then kept in a glass-stoppered bottle, the mouth of which was large enough to permit the removal of the powder with a spoon, taking care to avoid the inhalation of dead bacilli.

⁵ We are indebted to the Wyeth Corporation which, through the initiative of Dr. E. Shorr and with the helpful support of Dr. R. J. Dubos, provided us with 2 kg. of dried bacilli.

One hundred and fifty grams of dried ground bacilli were put in a large mortar; 450 cc. of mineral oil were measured out and just enough poured over the bacilli to wet them completely. This mortar was placed over a vessel of hot water (50° to 60°C.). Two or three small spoonfuls of the mixture at a time were removed to a small mortar and ground as well as possible with a large pestle. When the whole amount was well mixed, the rest of the 450 cc. of mineral oil was added, and the total was put back in the large mortar (still over the hot water) and then stirred with an electric stirrer for about one hour.

The fine suspension of bacilli in oil was then centrifuged in glass tubes at 3,500 R.P.M. for one hour. The supernatant was decanted and saved, and the residue of bacilli extracted a second time in the same way as before. This time, however, only 300 cc. of oil were added. When this extraction was finished, the mixture was centrifuged for one hour. Supernatant II was added to supernatant I. The residue was discarded.

A first centrifugation of the combined supernatants (I and II) was done in cellophane tubes in a Sorval angle centrifuge at 13,500 R.P.M. for one hour. The decanted supernatant was then put in new (bacilli free) cellophane tubes and centrifuged for four hours. Finally, the supernatant oil was taken out from the centre of the tubes with a 50 cc. pipette attached to a suction flask. The resulting oil is viscous, but perfectly clear and dark yellow-brown in color.⁶

The final amount of oil extract obtained from the original 150 g. of bacilli was about 500 cc.

Results with Oil Extracts

One single intraperitoneal injection of 1 cc. of this oil extract in guinea pigs established a definite tuberculin type hypersensitivity to Old Tuberculin; two successive injections at a fortnight's interval establish a high hypersensitivity.

The question arose as to whether this hypersensitivity was due to whole bacilli remaining in the oil. To eliminate this possibility, we decided to subject the oil extract, diluted with ether, to Berkefeld filtration (grade N filter). However, we did not know whether this sensitizing substance would be retained by the filter. First we diluted the oil ten times with ether, and the ether was removed by vacuum after filtration. The animals which received this Berkefeld filtrate, freed from ether by vacuum, became highly hypersensitized. Next we diluted the oil with an equal amount of ether, thereby making the solution more viscous and harder for any bacilli to pass through the filter. This filtrate was also passed twice more through the same filter. In every instance the resulting oil filtrate, when injected into normal animals, induced hypersensitivity.

When the biologically active substances were extracted from this Berkefeld filtered oil extract, the resulting yield of sensitizing substance was considerably less than that recovered from the unfiltered material. Nevertheless, once we knew that the Berkefeld filtrate of the oil extract, diluted with an equal amount of ether, contains an appreciable amount of the insoluble sensitizing substance, we adopted this method of filtering before the oil was subjected to extraction.

⁶ Part of the material which the oil contains must be in fine suspension, as revealed by examination in the dark field. This oil extract sometimes becomes cloudy when left standing for a few weeks, probably because the insoluble particles, coming in contact with each other by slow diffusion, produce large aggregates and settle to the bottom of the flask.

An equal amount of ether was added to the 500 cc. of oil extract and the total 1,000 cc. of oil-ether mixture was put through a Berkefeld filter. The ether was then evaporated by vacuum until only 10 per cent remained, making a final volume of 550 cc. (Aliquots of 200 cc. of the mixture were evaporated at a time in 500 cc. round-bottom flasks. The oil-ether mixture had a marked tendency to foam under vacuum.)

Extraction of Fractions from the Oil (Chart 2)

(1) *Precipitation with dioxane:* Five hundred ml. flasks were set up with well fitted corks, and in each flask were measured 50 ml. of the filtered oil extract. One hundred

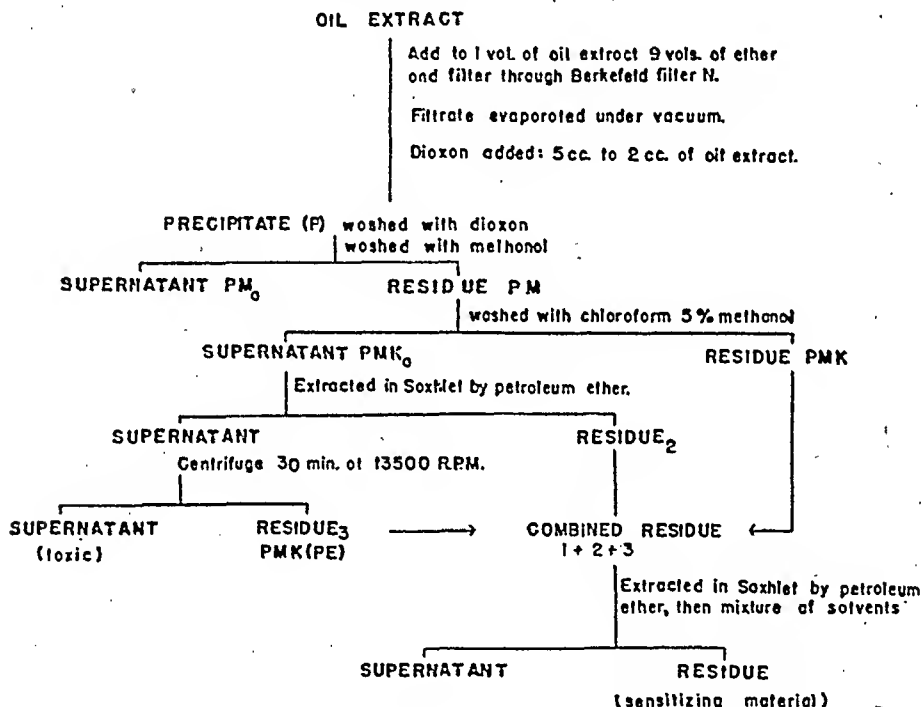


CHART 2. Extraction of fractions from the oil.

and twenty-five cc. of dioxane were added to each 50 cc. of oil, gradually with shaking. After ten to fifteen minutes, to allow precipitation to take place, 250 ml. more dioxane were added to each flask, all at once. The flasks were left overnight and the next day the supernatant was carefully decanted. The precipitate was then centrifuged in 90 ml. tubes, and the total finally collected in 4 tubes. It was then washed four successive times with clean dioxane to get rid of the oil. Each time, to the precipitate collected in the centrifuge tube was added clean dioxane little by little with stirring. After all the oil was removed, the material P was dried in vacuum.

(2) The dried precipitate P was then extracted with methanol. To this precipitate, 250 cc. of methanol were added. The insoluble part was collected by centrifugation, and washed with methanol until the solvent did not dissolve anything more from the precipitate.

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(5) The resulting insoluble part, P_M , was then extracted with a solution of chloroform containing 5 per cent methanol. To the P_M were added 300 cc. of this chloroform methanol solution. Most of the P_M seemed to be dissolved. It was then either put in a separatory funnel or filtered through a Soxhlet thimble. The clear fluid, P_{MKO} , was evaporated under vacuum in a round-bottom flask until dry. The insoluble part, residue 1, was saved.

In our first extractions, this P_{MKO} was our chloroform extract. But now from this P_{MKO} we extracted more residue. From the residue P_{MK} we recovered more P_{MKO} (last supernatant) as shown in chart 2.

(4) The dried P_{MKO} was then extracted in a Soxhlet apparatus with petroleum-ether. Some insoluble substance remained in the thimble (residue 2). The soluble part was centrifuged for thirty minutes in the Sorval angle centrifuge. The supernatant contains the final P_{MKO} , the so-called "toxic" material.

The insoluble part $P_{MK(PZ)}$ was added to the previous residues 1 and 2 and extracted in the Soxhlet with petroleum-ether once more and then with a mixture of solvents containing: petroleum-ether (2), ether (1.5), chloroform (1), ethanol (3), and methanol (1). During extraction with this mixture of solvents a white precipitate appears in the balloon of the Soxhlet. This precipitate is formed when the chloroform soluble part of the residue comes in contact with the methanol, in which it is insoluble. This shows that some P_{MKO} is still present in the "insoluble" residue P_{MK} .

This residue, taken from the Soxhlet thimble, was washed once more with petroleum-ether and collected by centrifugation. This final residue is the hypersensitizing fraction called fraction R.

The glassware used for these extractions was chemically cleaned. Furthermore, it was never used for any other purpose and had never been in contact with bacilli. All the solvents used were Eimer and Amend, C.P.

Each step in the washing of the insoluble material with the solvents was followed by the aid of the fluorescent lamp. Each solvent dissolves some substance which modifies its own fluorescence. The washing was stopped when the fluorescence of the supernatant was the same as that of the solvent itself. As the precipitate P is an aggregate of complex components, intimately combined, the use of a mixture of solvents was most helpful in their separation.

The yield from each of the successive extractions of 150 g. of bacilli was not always the same, even when the extraction was done in precisely the same way. There are probably many still unknown conditions of precipitation.

Our best yield of precipitate P was 3.6 g.; the average yield was about 2.5 g., that is 1.6 per cent of the weight of the dried bacilli extracted.

The "toxic" fraction was usually 50 per cent of the amount of P, while that of the sensitizing fraction was only one-thirtieth of the amount of P. From the 2 kg. of dried bacilli provided by the Wyeth Corporation, we were able to extract about 15 g. of the "toxic" fraction P_{MKO} and one gram of the hypersensitizing fraction R.

Properties of the "Toxic" Fraction

- (1) The "toxic" fraction P_{MKO} is easily soluble in chloroform, ether, petroleum-ether and benzene; insoluble in alcohol, methanol, dioxane and water.
- (2) It proved to be acid-fast and highly birefringent. It shows coloration in polarized light. Its melting point is 220° to 240° C.
- (3) The elementary composition as determined by William Saschek is:

C	H	N	P
53.84%	10.11%	1.05%	0.41%

No protein is detectable qualitatively. No quantitative determination has been made as yet, to find out if the nitrogen is related to proteins or to amino-acids.

This "toxic" fraction is a polysaccharide ester of the mycolic acid isolated by Anderson (17). Hydrolysis with 10 per cent potassium hydroxide in methanol separates it into sugars (water-soluble) and the mycolic acid (melting point 58° to 59° C.). Hydrolysis with 1 per cent sodium hydroxide in methanol separates it into sugars and the lactone of mycolic acid (melting point 47° C.). Mycolic acid and lactone can be obtained reversibly one from the other: by the action of concentrated sulfuric acid on the mycolic acid, the lactone is formed; when the lactone is treated with 10 per cent hydroxide solution in water, the mycolic acid is regenerated (16).

As mentioned above, *this carbohydrate-lipid complex has the remarkable capacity of producing lesions in the lungs* when injected into guinea pigs intraperitoneally, in paraffin oil. Such lesions are observable macroscopically ten days after injection, *even when the amount inoculated is as small as one gamma*. The pulmonary lesions are not identical with lesions produced by living bacilli. On a lung of a guinea pig, killed ten days after the injection of one gamma of the "toxic" component, suspended in paraffin oil, several gray nodules can be seen. Sections show abnormalities that are not found in lungs of guinea pigs injected with paraffin oil alone.⁷

For the inoculation of this substance into animals, a solution was first made in a few cubic centimeters of ether, in which it is soluble. The paraffin oil was then added to make a 0.5 mg. per cc. concentration in oil, and the ether removed under vacuum. The dilutions were made by adding warm paraffin oil to this homogeneous suspension.

The animals which received intraperitoneally a one-gamma suspension in paraffin oil of this material, when killed less than two weeks after the inoculation, already showed lesions in the lungs. With the passing of time, the lesions disappeared.

No such biological activity has ever been observed either with the mycolic acid alone or with the sugars alone, even when the normal animals received a dose of one mg. in paraffin oil, intraperitoneally.

Properties of the "Sensitizing" Fraction

The "sensitizing" fraction is a protein component, very insoluble in all the usual organic solvents, such as alcohol, methanol, chloroform, petroleum ether and benzene.

⁷ The author, who had returned to France, was asked to submit photomicrograms of these pulmonary lesions, but she was unfortunately not in a position to comply with this request, and she wrote that she thought that the study of these lesions should be left to pathologists. [Editor]

The chemical composition, as determined by William Saschek, is:

C
50.13%

H
7.75%

N
6.55%

P
0.46%

It has no melting point.

This "sensitizing" fraction is capable of establishing the true tuberculin type of hypersensitivity when injected, in paraffin oil, into normal animals.

Guinea pigs which receive two intraperitoneal injections of 0.1 mg. of this "sensitizing" fraction, in paraffin oil, become highly sensitive to the intracutaneous injection of Old Tuberculin. They react also to the whole intact bacilli.

The reaction of the hypersensitized animals to the intracutaneous injection of either OT or the intact bacteria is a delayed reaction, which appears only after several hours (more than six) and reaches a maximum size and intensity within twenty-four to forty-eight hours. This reaction is characterized by a swelling which is very much indurated. Necrosis of the skin, even hemorrhagic reactions, occurs sometimes in the highly hypersensitized animals. The reaction to 0.1 cc. of OT diluted ten times are usually at least 3+. The intensity of the reaction to OT is shown in figure 1. These pictures were taken thirteen days after the tuberculin test was made. (This particular date was a matter of convenience, as these animals were being photographed for other reactions on the same day.)

The state of hypersensitivity induced by this sensitizing substance remains for many months. In figure 2, one can see the response of these hypersensitized animals to the tuberculin test made more than five months after they had received their last injection of sensitizing material. The picture was taken seventy-two hours after the intracutaneous injection of 0.01 OT.

These hypersensitized animals do not react to the intraperitoneal injection of OT as do tuberculous animals. They do not die from the injection of 2 cc. of OT diluted ten times. They become sick for twenty-four hours, but they recover.

Passive transfer of this hypersensitivity from highly sensitized (4+) animals to normal animals was tried. We were never successful when we used the serum alone (one or two intraperitoneal injections of a few cc. each, at an interval of a few hours). But in 2 cases out of 10, when 4 to 5 cc. of the fresh whole blood of hypersensitized animals was injected intraperitoneally into normal animals, hypersensitivity could be demonstrated. A tuberculin test (with 0.1 cc. of OT diluted ten times), as well as a broth control test, was made thirty-six hours after the attempted passive transfer. The 2 animals, which were sensitized by passive transfer, reacted definitely to OT (1+); they did not react to the broth control.

We also succeeded (3 times out of 12) in sensitizing normal animals with an extract of organs (lungs and spleen) of hypersensitized animals. Each normal animal received intraperitoneally 6 to 10 cc. of the extract of the organs in saline of one hypersensitized animal. The tuberculin test, as well as a broth control test, was made on each animal thirty-six hours after the injection.

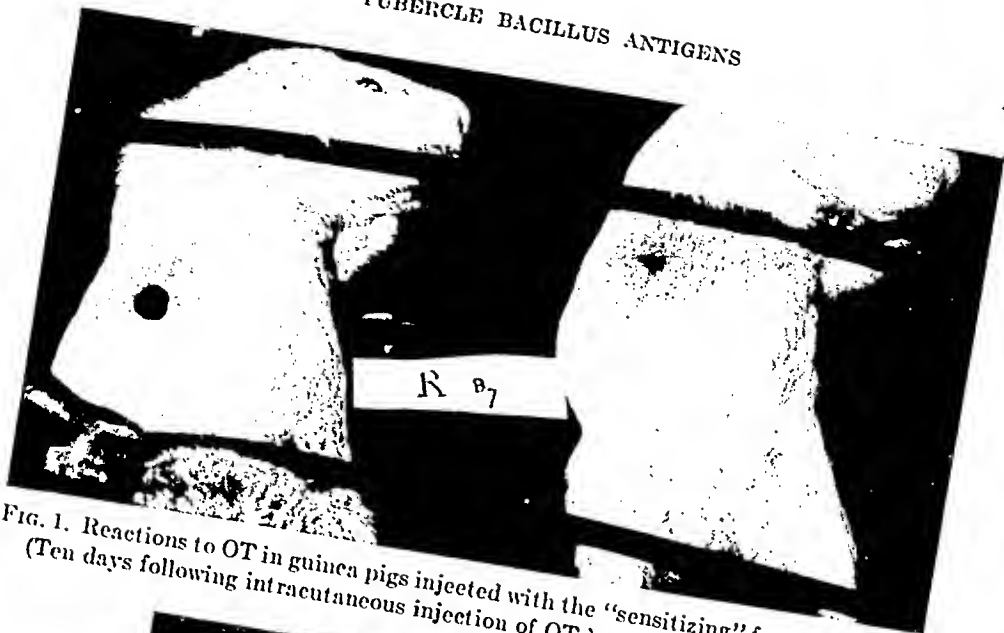


FIG. 1. Reactions to OT in guinea pigs injected with the "sensitizing" fraction in paraffin oil. (Ten days following intracutaneous injection of OT.)



FIG. 2. Tuberculin reaction in guinea pig, intraperitoneally injected with the "sensitizing" fraction more than five months before OT 1:100 was injected intracutaneously, seventy-two hours before this photograph was taken.

The 3 animals which were sensitized reacted definitely to OT (1+); they did not react to the broth control. After a few days, all the animals sensitized by cellular passive transfer ceased to respond to tuberculin.

We would not have referred to these few irregular successes on passive transfer of hypersensitivity, were it not for the fact that Chase (18) has demonstrated

clearly that tuberculin-type hypersensitivity is transferable with cells from sensitized to normal animals. Our observations can be said to have some value in the support of his demonstration.

We shall now describe further experiments which have been carried out, using as tools of investigation these two fractions of biological significance. These experiments revealed that the carbohydrate-lipid complex (which constitutes the "toxic" fraction) has the capacity of inducing antibody formation when injected into normal animals.

EXPERIMENT I

This first experiment was made when the work was taken up in the United States in an attempt to duplicate results on sensitization obtained by us in France (19).

TABLE 1
Summary of experiment I

GUINEA FIG NUMBER	INTRAPERITONEAL INJECTION 4/29/42	SKIN TEST WITH PPD			INFECTED INTRAPERI- TONEALLY WITH TUBERCLE BA- CILLI H-37 KAHN 2/9/43	DAYS OF SURVIVAL
		6/5/42	7/15/42	1/15/43		
118	1 cc. oil extract	+	+	+	0.5	320
162	0.1 mg. R	-	-	-	0.5	51
150	0.1 mg. R	+	+	+	0.1	*
160	0.1 mg. R	+	+	-	0.1	68
163	0.1 mg. R	+	+	-	0.1	90
90	1 cc. pure oil	-	-	-	0.5	36
16	1 cc. pure oil	-	-	-	0.5	61
52	1 cc. pure oil	-	-	-	0.1	80
57	1 cc. pure oil	-	-	-	0.1	58
58	1 cc. pure oil	-	-	-	0.1	65

* No. 150 was killed 11/18/44. No tuberculosis was found at autopsy.

We had at our disposal only 8 g. of dried dead bacilli, H-37 Kahn. From this amount, with the as yet unimproved technique of extraction, we were able to get only 1.2 mg. of residue ("sensitizing" fraction) and no appreciable amount of the "toxic" fraction.

Ten guinea pigs were immunized by intraperitoneal injection: 2 received 1 cc. of the whole oil extract, 8 received 0.1 mg. of the "sensitizing" fraction in 1 cc. of paraffin oil. Six weeks later all the animals were skin tested with OT and PPD. Eight of the 10 immunized guinea pigs were positive: the 2 which had received the whole oil extract and 6 of those which had received the "sensitizing" fraction only. The intensity of the reaction was not more than 1+.

Five of the 8 were still hypersensitive ten months later. Three of these 5 sensitized animals were killed, to establish that they were not tuberculous. The remaining 2, as well as the 3 which were no longer hypersensitive, and 5 controls, then received H-37 Kahn live bacilli (see table 1). All the animals

died within three months, except the 2 which were still sensitized. One of these, No. 118, which was infected with 0.5 mg. of bacilli, survived eleven months; at autopsy tubercle bacilli were found in all its organs. The other, No. 150, which received only 0.1 mg., was still alive and well at the end of nineteen months, at which time it was sacrificed. Doctor Opie was kind enough to do the autopsy on this animal. He found neither macroscopic evidence of tuberculosis, nor microscopic evidence in the sections which he later examined. The 2 surviving guinea pigs were skin tested several times after they were infected, and their strong reaction to OT left no doubt that they had received live bacilli.

We interpreted the result of this small experiment to be an indication that the "sensitizing" fraction, when separated from the other fractions of the bacilli, may act also as a protective antigen.

EXPERIMENT II

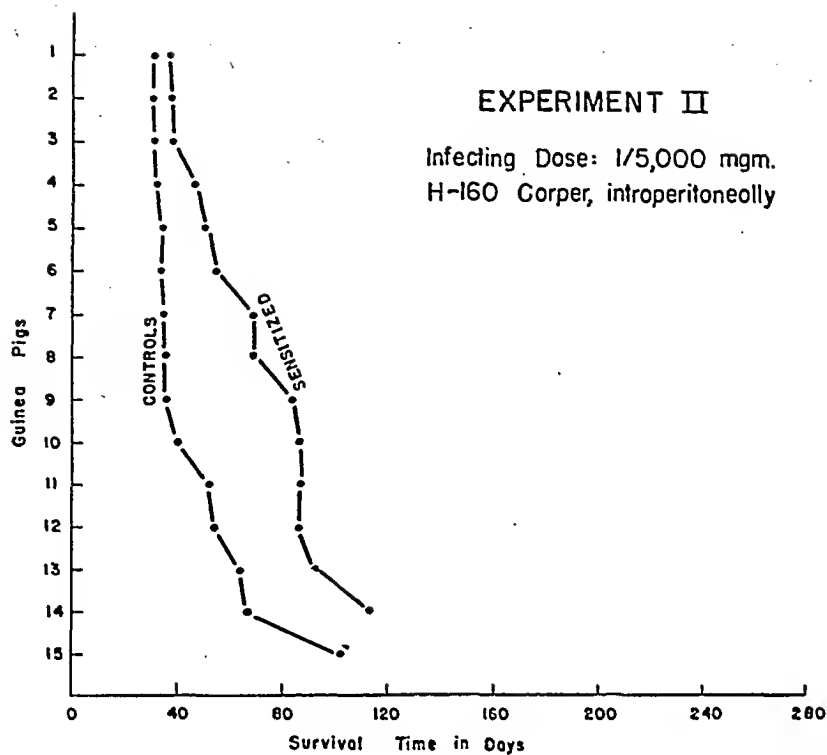
In the next experiment, we decided to infect the immunized animals with a strain of higher virulence than H-37, namely H-160 Corper. We were able, at that time, to obtain enough bacilli from our own cultures to make an extraction which yielded an appreciably greater amount of the "sensitizing" fraction. This fraction was purer than the one used in the first experiment.

Twenty-five normal guinea pigs were immunized by a single intraperitoneal injection of a paraffin oil suspension containing 0.1 mg. of this "sensitizing" fraction. Eighteen out of 25 were sensitized, although the intensity of the reaction to OT was not more than 2+. Only 15 of these were still sensitized five months later, at which time we decided to infect them.

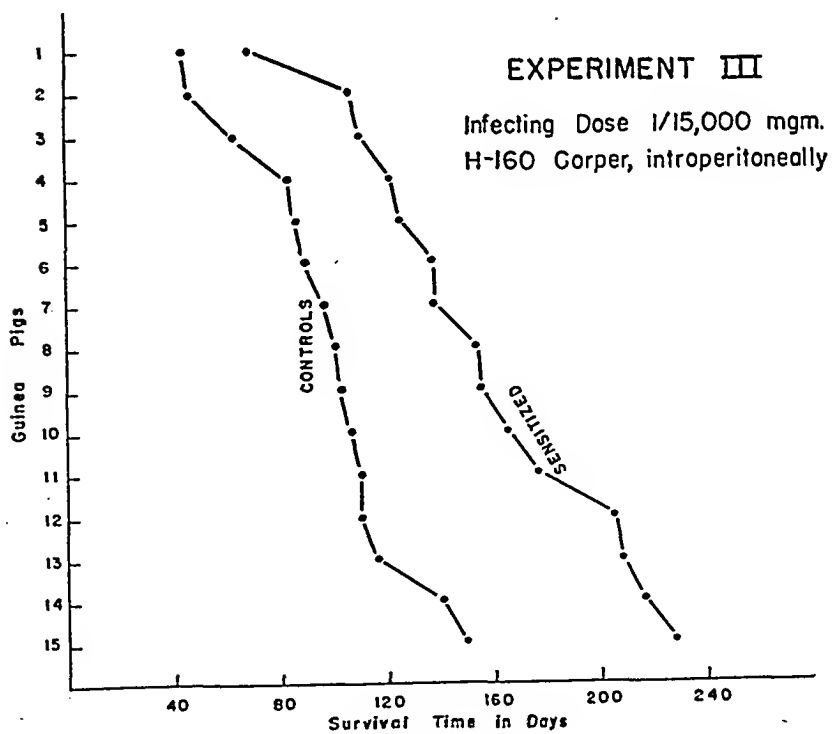
These sensitized guinea pigs, as well as 15 of the 25 controls, were then given intraperitoneally 0.0002 mg. of living bacilli H-160 Corper. We soon found out that the infecting dose was much too high. All the controls but one died within seventy days with generalized tuberculosis (see graph 1). The sensitized guinea pigs started to die somewhat later. The first ones to die had less tuberculosis than the controls. Those which died later had as extensive tuberculosis as the controls. We thought that the large infecting dose did not allow the previously observed mechanism of acquired resistance to become manifest.

EXPERIMENT III

This time, the infecting dose was only 0.000,067 (1/15,000) mg. of bacilli, H-160 Corper. The sensitizing antigen was the same as that used in experiment II. As we had found out in the meantime that two successive injections of 0.1 mg. of the "sensitizing" fraction, at a fortnight's interval, produced a high sensitization in all the guinea pigs which received it, we decided to employ this method of immunization in this experiment. Thirty animals were used. Fifteen controls received a single injection of paraffin oil alone. The course of the experiment can be seen in graph 2. This, at first, seemed to confirm the idea that the sensitized guinea pigs had some acquired resistance. Nine of the 15 controls were already dead with generalized tuberculosis, while



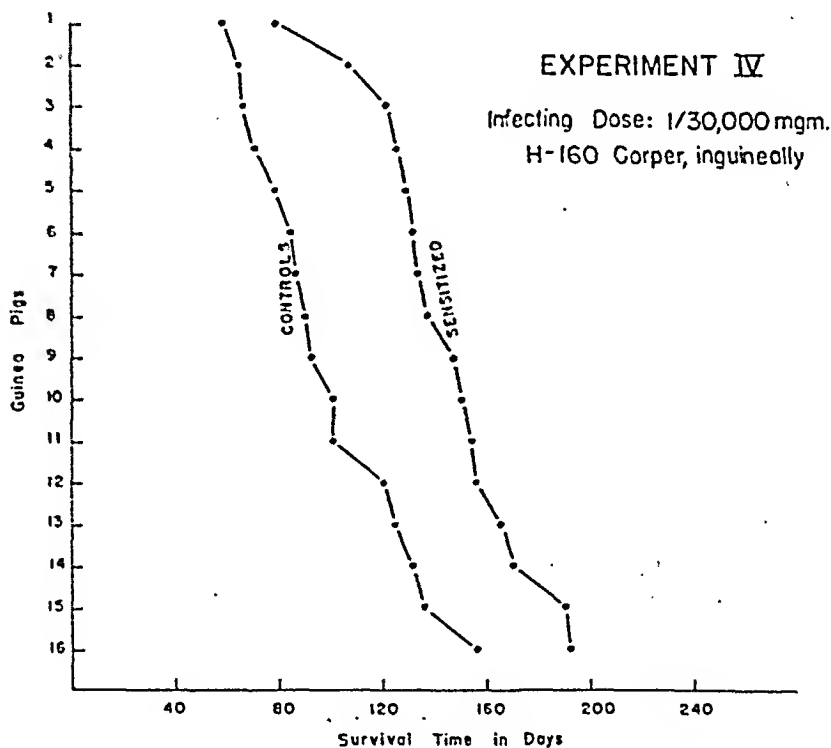
GRAPH I



GRAPH 2

all the sensitized animals, except one which died with almost no tuberculosis, were still in good health. These, then, began to die. The last four to die were still gaining weight until about two weeks before death. We found bacilli in all the organs of the sensitized animals, but in most of them there was less involvement than in the controls. The only striking difference between the two groups of animals was the size of the spleen. In the controls, the spleen was very much enlarged and caseous, while in the sensitized animals it was generally only slightly enlarged, with fewer caseous areas.

These differences and the longer survival period of the highly sensitized animals, compared to those of experiment II, led us to believe that a still lower infecting dose should be tried with the inguinal route of infection.



GRAPH 3

EXPERIMENT IV

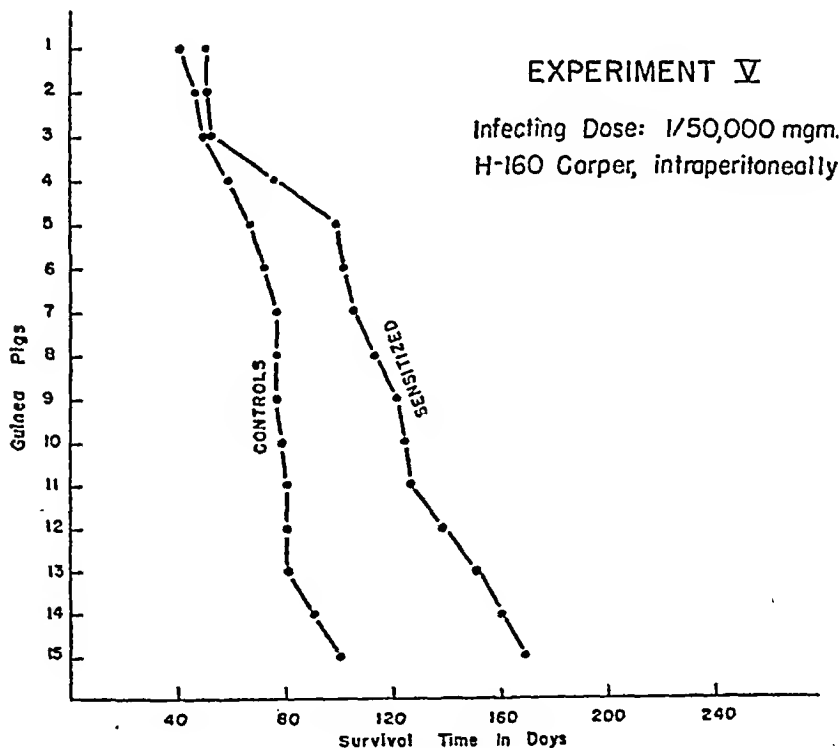
The immunized animals were infected inguinally with half the dose as that used in the preceding experiment, 0.000,033 (1/30,000) mg. of the strain H-160 Corper, following sensitization in the same manner as that in experiment III. The only difference was that the sensitizing fraction used for immunization in this experiment was *more purified* than that used in experiment III.

There were 32 animals in this experiment. All 16 animals immunized with this more purified "sensitizing" fraction reacted strongly to OT (3+ at least). Sixteen controls received a single injection of paraffin oil alone.

The course of the experiment can be seen in graph 3. In spite of the fact

that the infecting dose was lower; the hypersensitized animals showed less acquired resistance than those in experiment III. They all died from tuberculosis.

Once again, the only difference we could observe between the immunized animals and the normal controls was in the degree of involvement. The immunized animals showed less involvement than the controls, and again the spleens of the former were smaller and less caseous.



GRAPH 4

EXPERIMENT V

This time, the infecting dose was only 0.000,02 (1/50,000) mg. of bacilli, H-160 Corper, given *intraperitoneally*. The immunization of the normal guinea pigs was done in the same way as in the last experiment and with the same material.

Fifteen hypersensitized animals, which all reacted strongly to OT (3+ or 4+) two days before infection, and 15 normal controls were given live bacilli.

The course of the experiment (graph 4) was different from that of experiment IV. The 3 controls and 3 sensitized animals which died early had little tuberculous involvement in their organs. In the first animal (No. 1) to die in the sensitized group, we did not find any bacilli. In No. 2 and No. 3, very few bacilli were found in the lungs, none in the liver and the spleen was normal in size. In

the first 3 controls to die, bacilli were found in all the organs. Thus, the differences between hypersensitized and control animals were the same as in the other two experiments, except that the controls died sooner in experiment V than in experiment IV. We interpreted this finding as possibly due to the difference in mode of infection. In experiment IV, although the infecting dose of bacilli was considerably larger (1/30,000 in place of 1/50,000 of a mg.), infection was by the inguinal route instead of the intraperitoneal route.

Nevertheless, in spite of the fact that the infecting dose was lowered to 1/50,000 mg., and also in spite of the fact that in the last experiments the animals immunized with a pure "sensitizing" fraction developed a state of *higher hypersensitivity*, they failed to show the same degree of acquired resistance observed in experiment I. In this first experiment, as will be remembered, the animals were sensitized with a nonpurified material.

It was clear that something else in the "sensitizing" fraction, other than the sensitizing antigen, was responsible for the previously observed acquired resistance.

While these experiments on the relation of hypersensitivity (developed by the "sensitizing" fraction) to acquired resistance were being carried out, other experiments were being followed with the "toxic" fraction. The leading purpose in those experiments was to work out conditions under which the carbohydrate-lipid complex P_{MKO} would show the same lethal toxicity as that observed in France with the homologous substance extracted there. More than 150 guinea pigs were immunized with our P_{MKO} , more or less purified, combined or not with other fractions obtained from the paraffin oil extract. As was mentioned before, we were never able to duplicate the lethal effect.

But, when the animals immunized with our "toxic" fraction were subjected to the inoculation of living bacilli, to see how they would react to infection, they showed a better resistance than the controls, and in some instances much better resistance than the hypersensitized animals.

There were only two experiments, done on a small scale, for *preliminary investigation*. Each one, however, led us to believe that the carbohydrate-lipid complex, constituting our "toxic" fraction, might play an important part in the mechanism of acquired resistance.

Nine animals which in the past months had received either 2 gamma or 1 mg. of P_{MKO} in paraffin oil, intraperitoneally, one or two times, were given 1/30,000 mg. of bacilli, H-160 Corper, intraperitoneally, along with 10 controls. These immunized animals, when tested with OT three days before infection, were all negative to 0.01 OT.

In this experiment, all the controls were dead within eighty-five days. As may be seen in table 2, those animals which showed some acquired resistance had received either 1 mg. of P_{MKO} in one single injection, or two injections of 2 gamma each, at least four months before infection.

The other experiment (table 3) was carried out at the same time as experiment V on hypersensitivity, and with the same controls.

Among the animals which had been immunized with 2 gamma of the "toxic" fraction, 4 had received later a mixture of "toxic" and "sensitizing" fractions.

They all were injected intraperitoneally with 0.000,02 (1/50,000) mg. of bacilli of the strain H-160 Corper. In this experiment the immunized animals which received in a second injection the mixture of "toxic" and "sensitizing"

TABLE 2
Effect of "toxic" fraction on resistance of guinea pigs

GUINEA PIG NUMBER	"TOXIC" FRACTION mg.	DATE OF INJECTION	"TOXIC" FRACTION mg.	DATE OF INJECTION	SURVIVAL AFTER INJECTION IN DAYS	MONTHS BETWEEN FIRST INJECTION AND INFECTION
2538	0.002	10/11/44	0.002	12/15/44	77	3-
2541	0.002	10/11/44			91	3-
2553	0.002	10/11/44			83	3-
2511	1	9/18/44			113	4+
2508	1	9/18/44			137	4+
2509	0.002	9/18/44			156	4+
2567	0.002	9/18/44			121	4+
2510	0.002	12/30/43			82	4+
2233	0.002	12/30/43			99	12+
2229	1	12/30/43			159	12+
2228	1	12/30/43			132	12+

1/8/45 tubercle bacilli, H-160 Corper, 1/30,000 mg., were injected intraperitoneally in all guinea pigs.
All the controls (not listed) (10) died within eighty-five days after infection.

TABLE 3
Effect of "toxic" and "sensitizing" fractions on resistance of guinea pigs

GUINEA PIG NUMBER	TOXIC + R 4/1/45 mg.	OT TESTS 6/11/45	SURVIVAL TIME IN DAYS
1790	T 1/500 + R 1/10	+	156
1791		-	61
2371		-	82
2372		-	73
2379	T 1/500 + R 1/10	-	192
2362		(+ -)'	25
2404		-	177
2409		+	281

2/24/45 all animals received 0.002 mg. of toxic fraction.
3/23/45 all animals were tested with OT; none reacted.
6/14/45 tubercle bacilli, H-160 Corper, 1/50,000 mg., were injected intraperitoneally in all guinea pigs.

fractions survived longer than the other ones. Two of them showed a very good acquired resistance, greater than that observed with the highly hypersensitized animals of the same experiment V. This greater resistance could not be due to the presence of the "sensitizing" fraction by itself, since the ani-

imals highly hypersensitized with this fraction R did not develop the same degree of acquired resistance.

There are at least two possible explanations: (1) the protein contained in the "sensitizing" fraction behaves as a "carrier" for the "toxic" carbohydrate-lipid complex; (2) it may be that something yet unknown in the protein component that constitutes the "sensitizing" fraction, also plays a part in the mechanism of acquired resistance, when in combination with the "toxic" fraction. Only experiments involving a great number of animals would tell us about the mechanism of action of the "sensitizing" fraction when mixed with the "toxic" carbohydrate-lipid complex.

The fact remains that the "toxic" carbohydrate-lipid complex alone plays a part in the mechanism of the development of acquired resistance.

Moreover, there was evidence that the "toxic" material, the carbohydrate-lipid component, produces antibodies. Guinea pigs immunized with this "toxic" material, as well as animals infected with tubercle bacilli, reacted more to the intracutaneous injection of a few gamma of the "toxic" material than did normal controls.

Since this "toxic" material still contains some nitrogen, we wanted to be sure that the observed reactions were not a response to a very small amount of protein possibly contained in the "toxic" material. To obtain evidence on this point, the same animals were tested with both the "toxic" fraction and the "sensitizing" fraction, which contains seven times as much nitrogen as the "toxic" fraction.

The skin tests were made with 5 and 50 gamma of "toxic" material suspended in saline, in the right side of the shaved area of the animal, and with 5 and 50 gamma of the "sensitizing" material in the left side. The same tests were also made in normal animals and in animals infected with tubercle bacilli—3 of each kind being examined.

All treated animals reacted much more than did the normal controls to these intracutaneous injections.

Animals immunized with the "toxic" fraction reacted to 5 gamma of this "toxic" fraction, while they did not react to 5 gamma of the "sensitizing" fraction. They reacted more to the 50 gamma of the "toxic" than they did to the 50 gamma of the "sensitizing" fraction. These reactions showed that animals immunized with the "toxic" material—if they were reacting to a protein—reacted also, and to a greater degree, to something other than protein which is contained in our carbohydrate component.

The infected animals reacted even more to the "toxic" than they did to the same dose of "sensitizing" material. These observations suggested that the acquired resistance developed in guinea pigs by the "sensitizing" material was due to contamination of this material with the carbohydrate-lipid complex. This hypothesis received considerable support when we observed that the water soluble portion of the hydrolysate of our carbohydrate-lipid complex reacted, in precipitin tests, with the sera of rabbits and guinea pigs which had been injected with the "toxic" carbohydrate-lipid complex *alone*.

The hydrolysis was made in methanol 10 per cent potassium hydroxide. Five hundred mg. of the carbohydrate-lipid complex were dissolved in 5 cc. of benzene, and 20 cc. of the methanol potassium hydroxide solution were added to it. The hydrolysis proceeded for twelve hours at a temperature of 100° C. At the end, some water was added to dissolve the solid material adhering to the balloon, and all the material was extracted with ether in a separatory funnel. The water soluble part was washed many times with ether; the ether soluble part many times with water.

As was pointed out before, the ether solution contains the mycolic acid.

TABLE 4
Serological observations with oil extracts

ANTIGEN	RABBITS		GUINEA PIGS		RABBITS		HORSE
	No. 61	No. 26	No. 74	No. 49	Human Bacilli	Avian Bacilli	Human Bacilli
	Oil Extract	Carbohy- drate-lipid complex	Oil Extract	Carbohy- drate-lipid complex			
3.10 ⁻⁴	++++	+++	+++	+++	+++	+++	+++
3.10 ⁻⁵	++++	+++	+++	++	+++	+++	+++
3.10 ⁻⁶	+++	++	++	+	+++	+++	++
3.10 ⁻⁷	++	+	+	±	++	++	±
3.10 ⁻⁸	±	—	—	—	—	±	—
3.10 ⁻⁹	—	—	—	—	—	—	—

Rabbit No. 61 received 2 injections of 1 cc. each of oil extract, intraperitoneally, 19/9/44 and 3/12/46.

Rabbit No. 26 received 3 injections of 3 mg. each of *PMK₀* in 1 cc. paraffin oil, intraperitoneally, 3/14/45, 3/30/45 and 3/12/46.

Guinea Pig No. 74 received 2 injections of 1 cc. each of oil extract, Berkefeld filtered, intraperitoneally, 3/18/46 and 4/1/46.

Guinea Pig No. 49 received 2 injections of 100 gamma each of *PMK₀* in 1 cc. paraffin oil, intraperitoneally, 2/28/46 and 3/15/46.

Rabbits immunized with human and avian bacilli received 10 mg., in divided doses, of bacilli which were grown in Dubos' media.

Pure mycolic acid (melting point 58° to 59° C.) is obtained from the white substance contained in the ether solution, after several solutions in ether or benzene and precipitation with methanol or alcohol. The water soluble part of the hydrolysate contains the sugar. This solution appears to be a strong antigen.

This solution gives specific precipitin reactions with the sera of rabbits and guinea pigs which have been immunized by the whole oil extract, and also with the sera of animals which have been immunized by the "toxic" carbohydrate-lipid complex alone (table 4). Precipitations were obtained in dilutions as high as one in 10 million with some sera. Strong precipitations were also obtained with the serum of a horse which had been immunized with whole tubercle bacilli (serum kindly given to us by Dr. M. Heidelberger) and also with the sera of rabbits that had been immunized with human and avian tubercle

bacilli grown in the "Tween 80" medium recently described by Dubos and Davis (20).

Furthermore, the sera of rabbits immunized with the "toxic" carbohydrate-lipid complex alone in paraffin oil developed agglutinins, for human virulent and avirulent tubercle bacilli, to titres of over 1:1,000, as tested by the technique developed by Middlebrook (21).

This tuberculo-carbohydrate still contains 1.05 per cent of nitrogen. Perhaps this nitrogen could be eliminated with the use of better methods of purification. As pointed out before, we do not know as yet whether this amount of nitrogen is of protein nature or not, and amino sugars are known to be present in the carbohydrates of the tubercle bacillus (22). Whether this carbohydrate-lipid complex (protein free?) is a complete antigen or only a hapten is not yet known. But the serological reactions with the sera of animals immunized with this substance demonstrate, at least, that this tuberculo-carbohydrate is highly active in inducing antibody formation during the development of acquired resistance to tuberculous infection.

The serological reactions with the avian antisera, as well as the fact that an homologous carbohydrate-lipid complex could be extracted from bovine bacilli (Bovine Vallée) and even BCG, are a clear indication that no type-specificity analogous to that conferred upon the pneumococcus by its carbohydrates is to be expected for the tuberculo-carbohydrates.

This is the first demonstration that a carbohydrate-lipid complex of this nature, extracted from the tubercle bacillus, induces antibody formation when injected alone into normal animals. Whether or not this complex is a component conditioning the virulence of tubercle bacilli remains to be seen (23).

We wish to point out the fact that the higher titre of carbohydrate-antibody is found in the sera of animals immunized with the whole oil extract, which contains both the hypersensitizing fraction and the "toxic" fraction. On the other hand, in our explorative experiments, the animals which showed the best acquired resistance (table 3) were those which received not only the carbohydrate-lipid complex alone, but also in combination with a certain amount of hypersensitizing substance.

We believe that a high titre of carbohydrate-antibodies could be induced in normal animals immunized with a mixture of both "toxic" and "sensitizing" material, in such relative proportions that no state of hypersensitivity would be developed. The practical value of having these two fractions separated is obvious. They could be reassociated in the proper proportion to achieve the best degree of acquired resistance to tuberculous infection with the minimum degree of hypersensitization.

SUMMARY

Two fractions of biological significance have been isolated from paraffin oil extract of dead tubercle bacilli.

1. A proteinic component which seems to be the "sensitizing" antigen of the tubercle bacillus. This component has the power of establishing hypersensi-

tivity of the tuberculin type, when injected in paraffin oil, intraperitoneally, into normal animals.

2. A carbohydrate-lipid complex, chloroform soluble, which has the property of producing lesions in the lung of guinea pigs, when as small an amount as one gamma in paraffin oil is injected intraperitoneally. This carbohydrate-lipid complex has been found to have the capacity of inducing antibody-formation when injected into normal animals. The water soluble part of the hydrolysate of this antigenic component gives specific precipitin reactions with the sera of rabbits and guinea pigs which have been immunized with the whole oil extract, and with the sera of animals which have been immunized by the carbohydrate-lipid complex alone, and also with sera of animals which have been immunized with whole tubercle bacilli.

The preparation of the oil extract and the preparation from it of the antigenic components are described in detail.

Animal experiments on the relation of hypersensitivity to immunity established clearly that a high degree of hypersensitivity does not help the mechanism of acquired resistance, even when the state of hypersensitivity is induced in animals by the isolated "sensitizing" component of the tubercle bacillus.

Explorative experiments on the relation of carbohydrate-antibodies to immunity indicate that the carbohydrate-lipid complex might play a rôle in the mechanism of acquired resistance.

SUMARIO

Antígenos del Bacilo Tuberculoso: Propiedades Biológicas de Dos Sustancias Aisladas del Extracto de Aceite de Parafina de Bacilos Tuberculosos Muertos

Del extracto de aceite de parafina de bacilos tuberculosos muertos se han aislado dos fracciones de importancia biológica.

1. Un compuesto proteico que parece ser el antígeno "sensibilizante" del bacilo tuberculoso. Este componente posee la facultad de establecer el verdadero tipo de hipersensibilidad, al ser inyectado, en aceite de parafina, por vía intraperitoneal, en animales normales.

2. Un complejo lípido-hidrocarbonado, soluble en cloroformo, que posee la propiedad de provocar lesiones pulmonares en los cobayos, cuando se inyectan intraperitonealmente hasta cantidades que no pasan de un micrógramo, en aceite de parafina. Según se ha descubierto, este complejo lípido-hidrocarbonado posee la capacidad de evocar anticorpogénia al ser inyectado en animales normales. La parte hidrosoluble del hidrolizado de este componente antigénico da precipitino-reacciones específicas con los sueros de conejos y cobayos inmunizados con el extracto oleoso íntegro, y con los sueros de animales inmunizados por el complejo lípido-hidrocarbonado solo, y también con los sueros de animales inmunizados con bacilos tuberculosos íntegros.

Describense los pormenores de la preparación del extracto oleoso y de la preparación de los componentes antigénicos, del mismo.

Los experimentos en animales acerca de la relación de la hipersensibilidad

con la inmunidad establecieron claramente que la primera no ayuda el mecanismo de la resistencia adquirida, aun cuando se evoca el estado de hipersensibilidad en los animales con el componente "sensibilizante" aislado del bacilo tuberculoso.

La exploración experimental de la relación de los anticuerpos hidrocarbonados con la inmunidad indica que el complejo lípido-hidrocarbonado podría desempeñar un papel en el mecanismo de la resistencia adquirida.

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It gives me pleasure to express my gratitude to Dr. Michael Heidelberger for his encouragement and wise counsel, and to Dr. René Dubos for his constant support of our work.

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Finally, I wish to express my deep gratitude to all of those whose friendship and kindness helped me to keep up my courage during the dark days of the war before the liberation of France.

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STREPTOMYCIN IN EXPERIMENTAL TUBERCULOSIS¹

I. Its Effect upon a Well-Established Progressive Tuberculous Infection in Guinea Pigs

W. STEENKEN, JR. AND E. WOLINSKY

Many agents (1 to 14) have been used in an attempt to retard an early, as well as an established progressive tuberculosis in guinea pigs and other experimental animals. Streptomycin, discovered by Waksman and his coworkers (7), is by far the most effective agent to date in its activity against the tubercle bacillus in the test tube, as well as in the experimental animal. It is of such low toxicity as to be well tolerated in the animal body (14, 15, 16, 17, 18, 19).

It has been shown (13) that streptomycin, when added to various media in concentrations of 0.2 to 0.4 units per cc. of medium, inhibits the growth of tubercle bacilli *in vitro*. With these figures in mind, we decided to treat a group of guinea pigs with doses of streptomycin that would insure a blood level of at least ten times this growth-inhibiting concentration *in vitro* during the course of treatment, the duration of which was determined by our supply of the drug.

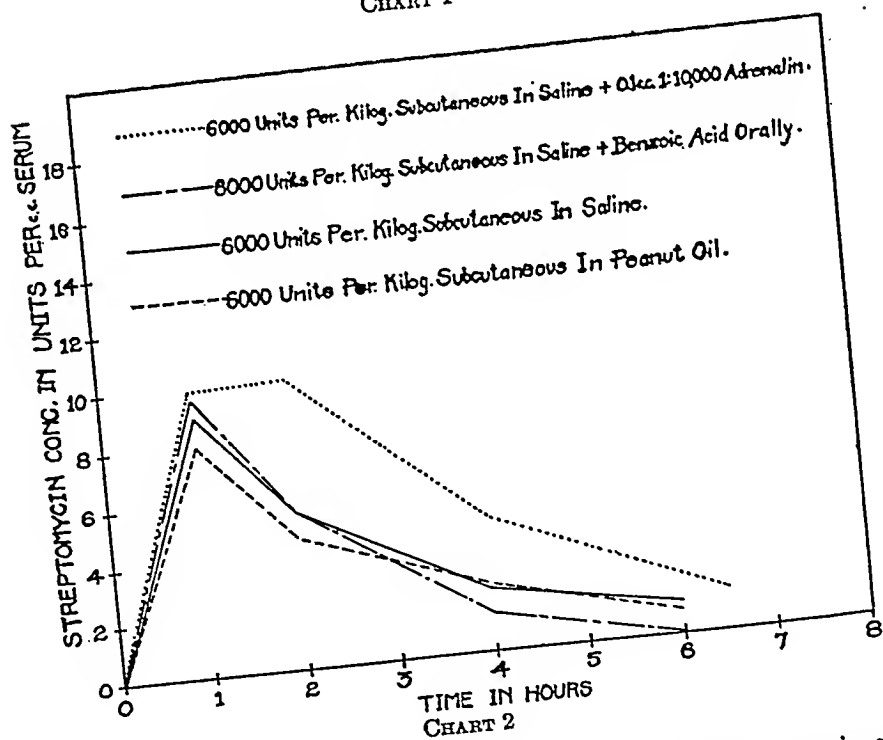
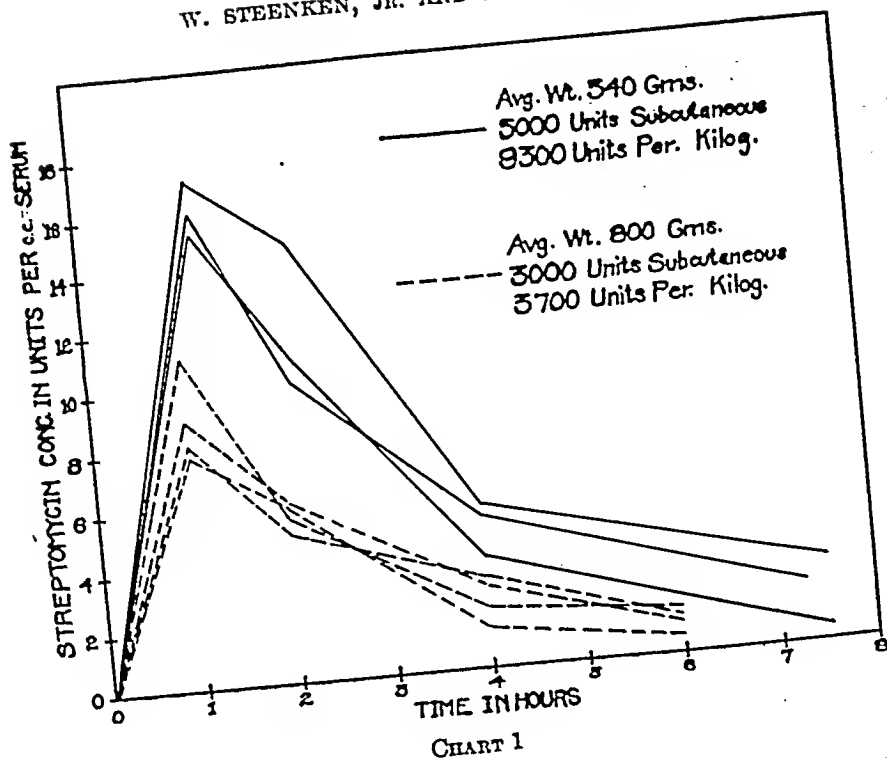
Before treating this group of animals with streptomycin, a study was made of the rate of absorption and excretion, and the blood levels obtainable with a given dose of the drug. This was done in order to judge the amount of the individual dosage and the number of doses per day necessary to produce an effective blood level. Streptomycin assays were done by the agar cup method of Stebbins and Robinson (21), which proved to be accurate and reliable for our purpose. The results are shown in charts 1 and 2.

Chart 1 shows the serum streptomycin levels in 7 guinea pigs, after a single subcutaneous injection of streptomycin hydrochloride. Maximum levels were obtained in one hour, with a rapid decrease thereafter up to four hours. Using the higher dosage of 9,300 units per kilogram, maximum levels were about 16 units per cc. of serum at the end of the first hour. Four-hour levels were about 3.5 to 5.0 and seven and a half-hour levels showed a trace to 3.0. With the lower dosage of 3,700 units per kilogram, one-hour levels were 7.5 to 11 units per cc. of serum, four-hour levels 1 to 3, and six-hour levels a trace to 1.5.

Chart 2 shows the results of attempts to prolong the absorption and excretion time of the streptomycin in the animal body by using the drug in peanut oil, in conjunction with benzoic acid by mouth, and together with adrenalin subcutaneously. The last method prolonged the serum level slightly, but not enough to warrant its use. The other methods were without effect.

In view of these results, it was decided to begin treatment with 24,000 units per day of streptomycin for each animal, given subcutaneously in doses of 4,000 units (about 5,000 units per kilogram) every four hours day and night. After twenty days of this intensive treatment, the dosage was reduced to 16,000 units per day—4,000 units at four-hour intervals from 9 a.m. to 9 p.m. This insured the desired blood level for at least sixteen hours of the day.

¹ From the Research and Clinical Laboratory, Trudeau Sanatorium, Trudeau, New York.



The following procedures were carried out in various groups of guinea pigs: Nine male guinea pigs, with an average weight of 630 g., were vaccinated

with three subcutaneous injections of 2.5 mg. of $H_{37}R_{\Delta}$ microorganisms, on alternate days, or a total of 7.5 mg. (22). All reacted to 5 per cent OT three weeks later.

Ten weeks after vaccination of these pigs, a group of 37 animals, including the 9 vaccinated and 28 normals, were infected by subcutaneous injection in the groin of 0.021 mg. dry weight of the human virulent strain, $H_{37}R_{\Delta}$. The inoculum was prepared from a ten-day growth of the microorganisms on Proskauer and Beck's synthetic medium by grinding in a mortar with a small amount of physiological saline, and the weight of microorganisms per cc. determined by evaporating one cc. to dryness on a water bath.

Forty-nine days after infection, treatment with streptomycin² was begun as outlined above on 14 nonvaccinated and 4 vaccinated guinea pigs. After forty days of treatment, 7 of the nonvaccinated-treated group were taken off treatment, and treatment was also stopped on the 4 vaccinated pigs. These animals, for which treatment was discontinued after forty days, were still alive eighty-eight days later, at which time they were sacrificed and the experiment terminated. The other nonvaccinated animals were continued on streptomycin for 125 days, or until the end of the experiment, when all surviving animals were killed.

The streptomycin ampule of one million units (1.0 g. of pure streptomycin base) was dissolved and diluted in 100 cc. of sterile distilled water, giving a concentration of 10,000 units per cc.; 0.4 cc. of this solution was injected subcutaneously to give a dosage of 4,000 units. For the first twenty-four days of treatment, Merck's streptomycin hydrochloride, Lot No. 280, 170 units per mg. was used. For the next sixty-four days, Lot No. 345, 250 units per mg. of the hydrochloride from Merck was injected. Streptomycin sulfate, Pfizer Lot No. 466, potency 423 units per mg. was used during the last thirty-seven days of treatment.

To summarize the groupings of the animals:

Group I—Vaccinated, treated forty days, 4 guinea pigs

Group II—Vaccinated, controls, 4 guinea pigs

Group III—Nonvaccinated, treated 125 days, 7 guinea pigs

Group IV—Nonvaccinated, treated forty days, 7 guinea pigs

Group V—Nonvaccinated, controls, 12 guinea pigs

To determine the degree of tuberculosis at different periods of time, one vaccinated animal was killed forty-nine days after infection, one nonvaccinated was sacrificed twenty-four days after infection, and one nonvaccinated sacrificed forty-nine days after infection.

RESULTS

The normal control animal killed twenty-four days after infection showed evidence of tuberculous disease in the spleen as well as in the inguinal and iliac lymph nodes on the side of inoculation. The nonvaccinated pig killed on the

²Streptomycin was supplied through the courtesy of Merck and Company, Rahway, New Jersey, and Charles Pfizer and Company, Brooklyn, New York.

forty-ninth day had a far advanced, wide-spread disease with maximal involvement of the liver and spleen, and many tubercles in the lung. The vaccinated animal which was killed on the forty-ninth day had tuberculosis only in the local lymph node at the site of inoculation. These sample killings indicated that, at the time treatment was started, most of the nonvaccinated animals had a wide-spread progressive tuberculous infection.

All 12 of the nonvaccinated controls (group V) died of wide-spread generalized tuberculosis of the lungs, liver, spleen and lymph nodes. The first animal succumbed sixty-nine days after infection (only twenty days after the treated groups were started on streptomycin) and the last animal 140 days from the date of infection. The average survival time was 103 days, and the average degree of tuberculosis as seen grossly on autopsy was 16 plus.⁸ Microscopically, these controls showed large areas of caseous pneumonia in the lungs, completely caseous and infarcted spleens, and massive caseation in the liver and lymph nodes.

None of the guinea pigs in any of the other groups died, including the vaccinated controls and the three streptomycin-treated groups. The surviving animals were killed and autopsied 175 days after infection.

The 4 vaccinated controls (group II) had a slowly progressive, but advanced, caseous type of disease, with an average degree of tuberculosis of 10 plus. Microscopically, the organs showed wide-spread proliferative and caseous tuberculosis in all but one animal, which exhibited caseation in the hepatic node only, with fibrous and proliferative tubercles elsewhere.

The group IV animals, which were treated for forty days, then allowed to live for eighty-eight days without treatment, showed a pathological picture similar to the vaccinated control group. They had wide-spread, slowly progressive proliferative tuberculosis, with an average degree of 11 plus. The spleens usually contained many large nodular tubercles, the lungs and livers a few scattered fibrous tubercles. Microscopically, these organs contained large, discrete, proliferative tuberculous lesions with caseation.

The animals in group III, which were treated continuously for 125 days up to the time of autopsy, showed extremely little grossly detectable disease, aside from a few small residual caseous nodes with fibrous capsules at the site of inoculation. The spleens in many of the animals were shrunk and adherent to surrounding structures and, microscopically, showed either no lesions at all or small areas of caseation surrounded by fibrous walls. One of these areas was calcified. The livers grossly revealed no tuberculosis. Microscopically, they showed increased portal connective tissue and portal lymphocytosis only. In the lungs, a few tiny, gray pitted areas could be seen grossly in most of the animals. On section, these proved to be small scars, and in addition there were scattered foci of lymphocytes. The average degree of tuberculosis was 1 plus.

* For the purpose of record and comparison, the involvement of the spleen, liver, lungs and lymph nodes was noted and individually assigned values were given proportionate to the extent and severity of the tuberculosis. The maximum rating of 4 in any organ was used to indicate wide-spread caseous disease diagnosed by gross inspection. The maximum value of 16 for the animal as a whole signified advanced generalized tuberculosis.

Chart 3 records the average degree of tuberculosis for each of the five groups of animals in the lungs, liver, spleens, and lymph nodes, as seen by gross inspection.

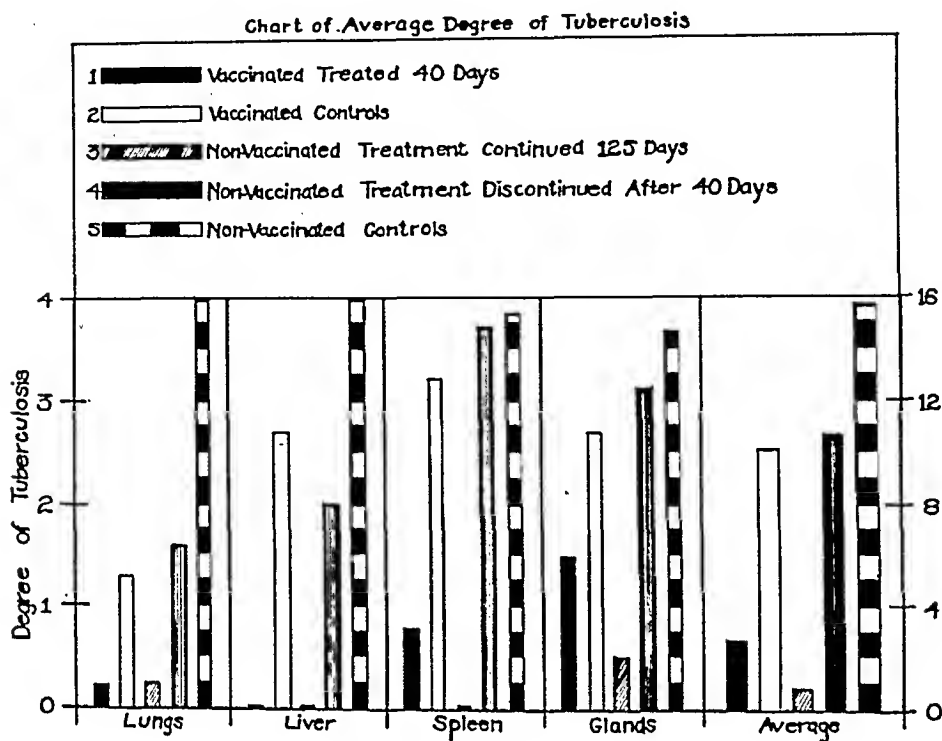


CHART 3

In figure 1 are reproduced the unretouched photographs of the organs of a typical animal from each of the nonvaccinated groups.

CLINICAL EVALUATIONS

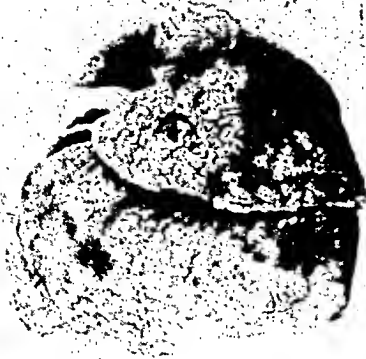
At the time treatment was started (forty-nine days after infection), it was obvious that all the nonvaccinated animals were losing weight, most of them had enlarged inguinal nodes and 6 had frank ulceration at the site of inoculation. The vaccinated animals were still gaining weight and none had inguinal ulceration. During the first twenty days of intensive treatment, all 3 guinea pigs which had ugly inguinal ulcers showed complete healing of these ulcers, while in the untreated normal controls, the 3 ulcers already present became worse (one animal died) and 2 more pigs developed frank ulceration.

After the twentieth day of treatment, none of the treated animals developed local ulceration. Of the 4 vaccinated controls, all eventually showed inguinal ulcers, and of the 12 nonvaccinated controls, 7 developed these ulcers at some time during their lives. In all these untreated animals, the ulcers progressed steadily, once they appeared.

It was noted that in the nonvaccinated groups the weights decreased gradually



A



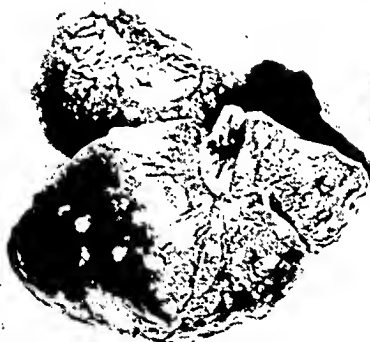
B



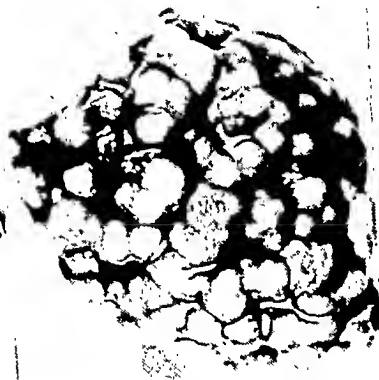
C



D



E



F



G



H



I

FIG. 1
232

in the seven weeks between infection and the beginning of treatment. During the first week of treatment (groups III and IV), the weight curve dropped precipitously, representing an average loss of 100 g. In order to evaluate the cause of this sudden loss of weight, a group of 5 normal young pigs were injected subcutaneously with sterile saline on the same schedule as the streptomycin-treated pigs. All these animals continued to gain weight during seven days of this treatment, which shows that handling and injecting the animals was not responsible for the sudden loss in weight. The vaccinated-treated group also lost an average of 95 g. during this first week of treatment, while the vaccinated controls lost only 23 g. and the nonvaccinated controls 35 g. In view of these findings, it seems to us that possibly a rapid destruction of many tubercle bacilli at the beginning of the intensive streptomycin therapy caused a massive tuberculinization of the animal with a consequent loss in weight.

During the second week of treatment, groups III and IV retained their weights, and from then on, gained progressively. The nonvaccinated controls never showed a real gain in weight.

The animals in group IV, in which treatment was discontinued after forty days, kept pace with group III (treatment continued) for nine weeks after treatment was stopped, but after that time they began to lose weight until they were killed.

The average weights for the vaccinated groups were unreliable because of the small number of animals in each group, but they show similar trends to the nonvaccinated groups.

All the untreated animals developed palpable inguinal lymph nodes, which became larger as time went on. In the treated pigs, these local nodes, which were present in all by the time streptomycin therapy was started, receded in size. After 125 days of treatment, 2 animals had no palpable nodes, 4 had very small, firm nodes about the size of buckshot, and one had a local tuberculous abscess. Eighty days after treatment was stopped in group IV, all 7 pigs had small inguinal nodes, firm and varying in size from buckshot to a small pea.

Aside from the first week, when they lost weight rapidly and were somewhat listless, the streptomycin-treated pigs appeared to be in good health throughout the experiment.

FIG. 1. Photographs of typical spleens, livers and lungs of guinea pigs.

Top row: Nonvaccinated control. A—Lungs: very many large tubercles. B—Liver: completely involved in tuberculous process. C—Spleen: very large, hemorrhagic and necrotic.

Middle row: Normal, treated for forty days, no treatment for eighty-eight days. D—Lungs: scattered small tubercles. E—Liver: many small tubercles. F—Spleen: many large nodular tubercles.

Bottom row: Normal, treated continuously for 125 days. G—Lungs: no gross lesions visible. H—Liver: no gross lesions visible. I—Spleen: small, fibrous appearance with a markedly constricted area, no gross tuberculous lesions visible (one-quarter has been removed for subinoculation).

SKIN SENSITIVITY TESTS WITH OLD TUBERCULIN

Throughout the experiment, skin tests with 5 per cent OT were frequently done.

Chart 4 represents the results of these tests in graphic form for all the non-vaccinated animals. For a reaction of 3 plus or over, central necrosis was required. One plus or less represented a reaction of not more than 5 by 5 mm., consisting of erythema and induration. Reactions were read after forty-eight hours. The chart reveals the following significant findings: All animals were tuberculin-negative before infection; one month later, just before treatment was started, all the pigs had positive tests of over 3 plus. The untreated animals

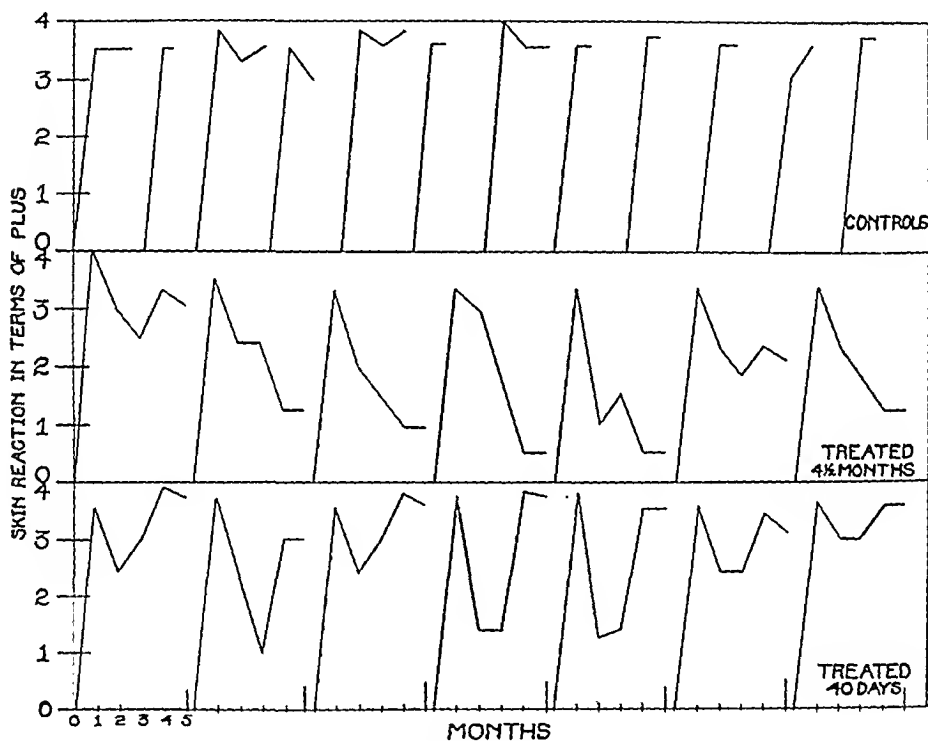


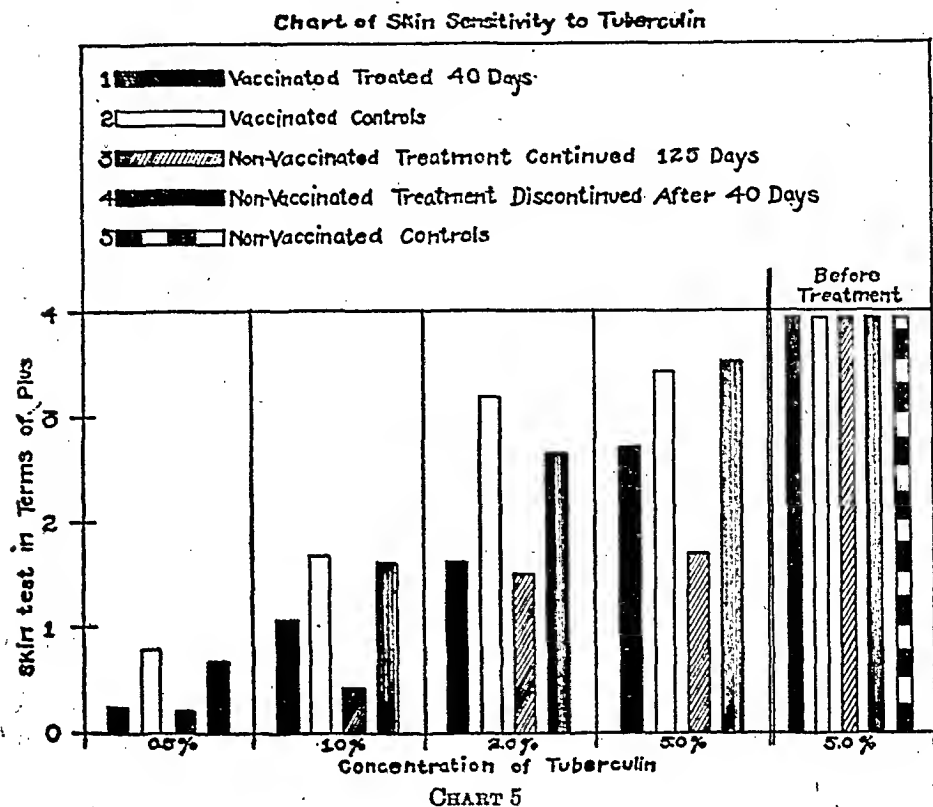
CHART 4

all remained highly positive until death. In the group treated for forty days only, the skin sensitivity in the second month, or after thirty-four days of streptomycin therapy, showed a decrease in all animals, in some more than others, but in all except one to below 3 plus, and in one to 1 plus. One month after treatment was stopped, the skin sensitivity began to show a return to the previous high level.

In the guinea pigs treated continuously for 125 days, the tuberculin reactions showed a progressive decrease in intensity from the second month to the end of the experiment. (The one animal excepted, whose sensitivity remained at 3 plus, was found to have a persistent, local tuberculous abscess near the site of inoculation.) In only 2 of the 7 animals, or 28.6 per cent in this group,

did the skin test become so decreased as to be read as doubtful. Feldman *et al.* (14) reported that 39 per cent of their guinea pigs, which had been treated for 166 days with streptomycin, did not react to tuberculin. Smith and McClosky (16) reported that all pigs treated for seventy-six to ninety-two days with streptomycin (but given only 5,000 units once a day) remained positive to PPD.

Chart 5 records the degree of skin sensitivity of the animals in the various groups tested with 0.5, 1.0, 2.0 and 5 per cent OT near the end of the experiment.



It demonstrates that a concentration of not less than 2.0 per cent and preferably 5 per cent by volume should be used in skin testing guinea pigs. Loss of skin sensitivity may be reported if such precaution is not taken.

STREPTOMYCIN BLOOD LEVELS

After receiving 4,000 units of streptomycin every four hours day and night for two weeks, blood was withdrawn from the hearts of 3 guinea pigs four hours after the last dose of the drug. This represented the minimum streptomycin level in the serum during the twenty days of intensive therapy. The results obtained were 3.0, 6.0 and 7.5 units per cc. of serum, respectively. According to the weights of the animals at that time, the dosage of 4,000 units of streptomycin represented 5,500 units per kilogram.

After 125 days of streptomycin therapy, blood was withdrawn from 6 of the remaining animals at one-hour and four-hour intervals after the 9 a.m. injection of 4,000 units of the drug. These animals had received no drug since 9 p.m. the previous evening. The one-hour levels were 7.0, 8.0, 8.0, 9.0, 10.0 and 13.0 units per cc. of serum. The four-hour levels were trace, 1.2, 1.2, 1.5 and 1.8 units per cc. of serum. One animal died during bleeding, which accounts for only five determinations at the four-hour period.

The higher levels obtained on the earlier titration may be explained by the fact that there was some accumulation of streptomycin in the serum when injections were given every four hours, and the animals were smaller at that time and therefore received more units per kilogram body weight.

TABLE 1

Results of subinoculation of organs of guinea pigs treated with streptomycin

GUINEA PIG NUMBER	GROUP	LAST TUBERCULIN TEST	SUBINOCULATION	
			Pig No. 1	Pig No. 2
1	Group III treated 125 days	2 plus	+	+
2	Group III treated 125 days	3 plus	—	—
3	Group III treated 125 days	4 plus	—	—
4	Group III treated 125 days	1 plus	+	+
5	Group III treated 125 days	2 plus	+	+
6	Group III treated 125 days	2 plus	+	+
7	Group III treated 125 days	1 plus	—	+
8	Group IV treated 40 days	4 plus	+	+
9	Group IV treated 40 days	3-4 plus	+	+
10	Group IV treated 40 days	4 plus	+	+
11	Group IV treated 40 days	4 plus	+	+
12	Group IV treated 40 days	4 plus	+	+
13	Group IV treated 40 days	4 plus	+	+
14	Group IV treated 40 days	3-4 plus	+	+

SUBINOCULATION

When the surviving animals were killed, attempts were made to determine the presence or absence of viable tubercle bacilli by culturing and subinoculation into guinea pigs portions of various organs. From group III animals (treated 125 days) and group IV animals (treated forty days), good-sized portions of the spleen, liver, lungs and lymph nodes, always including all suspicious areas of tuberculosis in these organs, were ground to a pasty mass in a sterile mortar with the least possible amount of physiological saline. The material was divided in two, one-half was injected directly into the groins of 2 normal guinea pigs, and the other half was treated with 4 per cent sodium hydroxide and carried through the regular routine concentration procedure. The resultant sediment was seeded on solid egg-yolk-potato-flour media. (Media recently recommended by the Committee on Evaluation of Laboratory Procedures of the American Trudeau Society.)

The results of subinoculation into guinea pigs are recorded in table 1.

It will be noted from table 1 that 5 out of 7 guinea pigs treated with streptomycin continuously for 125 days still harbored viable tubercle bacilli, while the organs from all the animals treated for only forty days produced subinoculation tuberculosis. It will be observed also that the severity of the skin reaction, even though the animals were injected with virulent tubercle bacilli, did not necessarily parallel the amount of subinoculation tuberculosis. It is interesting to note that animal number 3 had a small caseous abscess at site of inoculation in the inguinal region. This was removed, just prior to killing the animal, for culture of tubercle bacilli for sensitivity studies. The high degree of skin allergy in this animal could have been attributed to this focus of infection, and with the removal of the abscess the source of the remaining tubercle bacilli was eliminated.

DISCUSSION

The results reported in this paper confirm the observations of Feldman *et al.* that, when streptomycin is administered intramuscularly or subcutaneously to guinea pigs that have an advanced progressive tuberculosis produced by H₃₇R_v microorganisms, it not only retards, but brings about a marked healing of the disease process. This healing is more marked than has hitherto been seen in this laboratory when other drugs were employed in an attempt to retard a progressive tuberculosis. At this point, several observations are worthy of emphasis:

1: As demonstrated previously in this paper, skin allergy was suppressed or altered in most of the treated animals; in other words, the reaction was minimal or almost nonspecific in 4 out of 7 animals when they were skin tested with 5 per cent OT after streptomycin treatment.

2: Tissues from these animals with an almost negative tuberculin reaction produced subinoculation tuberculosis.

3: Tissues from some animals that demonstrated a moderate degree of skin sensitivity, failed to produce subinoculation tuberculosis in guinea pigs. We believe that the reason for the failure to produce subinoculation disease with tissues from one animal (number 3) was probably due to the fact that we had removed a small subcutaneous tuberculous abscess from the site of inoculation one week prior to terminating the experiment. We removed this small, well-walled-off lesion in order to use it for culture. Unfortunately, we did not skin test this animal after removal of the lesion to determine whether or not its skin allergy was altered. The other animal (number 2) probably had a lesion somewhere in a tissue not removed for subinoculation and overlooked at autopsy.

4: At autopsy, animals treated for forty days only, showed grossly and microscopically a chronic type of disease quite similar to the vaccinated animals.

This type of chronicity can be observed in any group of animals that has been vaccinated with living attenuated tubercle bacilli prior to infection. Whether or not the animals that were treated 125 days would have developed a progressive disease after the drug was interrupted is still unanswered by this experiment. The authors feel quite certain that these animals would have developed a progressive disease as long as they harbored viable virulent tubercle

bacilli. Whether the progression of the disease will be the same in the animal that has become relatively desensitized as contrasted with the still fairly allergic animal, will be reported in a subsequent study.

The $H_{37} R_v$ tubercle bacilli did *not* develop streptomycin resistance during the forty or the 125 days of therapy of any of the animals. This will be reported in greater detail in another paper. This may explain why there is such a rapid and marked resolution of the disease in guinea pigs; as contrasted with humans in whom the tubercle bacillus develops an increased resistance to the drug rather rapidly.

SUMMARY

$H_{37} R_v$ microorganisms, 0.021 mg. dry weight, were injected subcutaneously into 34 guinea pigs; 8 previously vaccinated with $H_{37} R_a$ and 26 normal animals. Forty-nine days later, when the disease was well established, streptomycin treatment was started on 14 nonvaccinated and 4 vaccinated animals. Each treated pig was given 24,000 units (micrograms) per day subcutaneously, in doses of 4,000 units every four hours, for twenty days. The dosage was then reduced to 16,000 units per day, given as 4,000 units every four hours from 9 a.m. to 9 p.m. After forty days of treatment, half of the nonvaccinated-treated animals and all 4 vaccinated animals were taken off treatment and allowed to live for another eighty-eight days. At the end of this period, 175 days after infection, and 125 days after treatment was started, the experiment was terminated by sacrificing all surviving animals.

All the nonvaccinated controls died of tuberculosis within sixty-nine to 140 days. None of the treated pigs, and none of the vaccinated controls, died during the 175 days of the experiment. The animals treated continuously for 125 days showed very little tuberculous disease at autopsy. Virulent tubercle bacilli were recovered from 5 of these 7 pigs by subinoculation. The animals treated for forty days only, demonstrated a slowly progressive, chronic type of tuberculosis at autopsy, similar to that of the vaccinated controls, and virulent tubercle bacilli were recovered from all 7 by subinoculation and subculture.

CONCLUSIONS

1. Streptomycin is an agent which has a definitely beneficial and curative effect on a well-established, advanced tuberculosis in guinea pigs.

2. Animals treated with streptomycin for forty days still harbor virulent bacilli, and develop a slowly progressive, chronic type of tuberculosis when treatment is stopped.

3. Of 7 animals treated continuously for 125 days, 5 still harbored virulent tubercle bacilli as demonstrated by subinoculation; one had a persistent local tuberculous abscess as the only demonstrable tuberculous focus.

4. The vaccinated pigs treated for forty days only, had less disease when killed eighty-eight days later than the nonvaccinated animals treated the same length of time.

5. Local skin ulceration at the site of inoculation healed rapidly with streptomycin treatment.

6. Skin sensitivity to 5 per cent OT decreased consistently during streptomycin treatment, and after 125 days of treatment 2 of the 7 animals had reactions of only 5 by 5 mm. erythema.

7. Streptomycin in doses as high as 24,000 units a day was apparently well tolerated by the guinea pigs.

CONCLUSIONES

La Estreptomicina en la Tuberculosis Experimental: I. Efecto sobre una Infección Tuberculosa Evolutiva bien Establecida en el Cobayo

1. La estreptomicina es un elemento que ejerce un efecto decididamente beneficioso y curativo sobre la tuberculosis avanzada bien establecida en los cobayos.

2. Los animales tratados con estreptomicina durante 40 días todavía albergaban bacilos virulentos, y desarrollaron una forma crónica y lentamente evolutiva de la tuberculosis al suspenderse el tratamiento.

3. De 7 animales tratados continuamente por espacio de 125 días, 5 todavía albergaban bacilos tuberculosos virulentos, según se demostró por medio de la subinoculación; uno mostraba un absceso tuberculoso local persistente como único foco tuberculoso observable.

4. Los cobayos vacunados tratados solamente durante 40 días mostraron menos enfermedad al matarlos 88 días después que los no vacunados tratados durante el mismo período de tiempo.

5. La ulceración cutánea local en el sitio de la inoculación sanó rápidamente con la estreptomicinoterapia.

6. La sensibilidad cutánea a la TA al 5 por ciento disminuyó constantemente durante el tratamiento con estreptomicina, y al cabo de 125 días de tratamiento en 2 de los 7 animales la reacción consistía únicamente en eritema de 5 por 5 mm.

7. La estreptomicina, a dosis hasta de 24,000 unidades diarias, fué aparentemente bien tolerada por los cobayos.

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THE REDUCTION OF POTASSIUM TELLURITE BY MYCOBACTERIUM TUBERCULOSIS¹

L. ŠULA

We have still little knowledge of the biochemical characteristics and the metabolism of *Mycobacterium tuberculosis*. Most pathogenic microbes require special media for primary isolation from infected material and for growth in pure cultures. The tubercle bacillus, however, grows in pure cultures on simple synthetic media, such as Long's, Sauton's, Lockemann's and others, and does not require any vitamins, provided that a large enough inoculum is transplanted to the surface of the synthetic medium. There is no need to add the known bacterial vitamins, such as panthoten, pimelic, p-amino-benzoic acid, biotin, etc. to the synthetic culture medium. So far, we have no information about the ferment system enabling the tubercle bacillus to build up complex proteins, lipids, high molecular fatty acids, flavins, etc. from simple and chemically exactly defined substances in synthetic media. Compared with the great synthesizing ability of the tubercle bacillus, its hydrolytic abilities seem insignificant: it does not ferment sugar, it does not form indol, H_2S , nor does it liquefy gelatin or dissolve hemoglobin. Its growth in pure cultures does not require proteins or the products of its break-down; a sufficient oxygen supply, glycerin, asparagin and a few simple anorganic salts are able to cover its nutritive and metabolic requirements. Therefore, any reaction enabling us to gain deeper insight into the complicated metabolic processes of tubercle bacilli, especially those concerned with the requirements of growth, deserves particular attention.

The present paper deals with a reaction which was described in 1905 by Gosio (2) and in 1915 investigated in regard to tubercle bacilli by Corper (1). The capacity of reducing potassium tellurite to metallic tellurite is called by Corper the tellurite test. The mechanism involved is the reduction of aqueous solutions of potassium tellurite to tellurium, similar to the reaction of the *Corynebacterium diphtheriae* on Clauberg's medium.

METHODS

For isolating tubercle bacilli from infected tissues, sputa, etc. a liquid ascites medium (Šula (6) 1946) was used. Its formula is as follows:

Dibasic sodium phosphate + $12H_2O$	2.5 g.
Monobasic potassium phosphate.....	1.5 g.
Magnesium sulphate + $7H_2O$	0.5 g.
Sodium citrate (neutral).....	1.5 g.
Ferric ammonium citrate.....	0.05 g.
Asparagin.....	3.0 g.
Glycerin.....	20 cc.
Water q.s.ad.....	1,000 cc.
Malachite green — 0.2 per cent aqueous solution.....	1.0 cc.

¹ From the Laboratory for Tuberculosis, State Institute of Public Health, Korunní 158, Prague XII, Czechoslovakia.

This solution is autoclaved at 120°C. for twenty minutes and then cooled; 100 cc. of human ascites, sterilized by filtering through a Seitz filter, is added; 5 cc. of the medium is poured into sterile tubes and the level of the fluid is marked on the wall of the tubes. The tubes are closed with cotton plugs.

The test tubes with 5 cc. of ascites medium were inoculated with laryngeal swabs from patients examined for tuberculosis at the State Institute. The tubes were incubated at 37.5°C. for three weeks. After this time the tubes showing positive results were divided in three parts. One part was submitted to the tellurite reaction immediately, another part was left in the incubator for six weeks and the last part for five months. Generally, ascites fluid medium is used in our laboratory for isolation of tubercle bacilli. Comparison with the Löwenstein-Jensen medium showed that ascites medium is equally sensitive and especially suitable for isolating tubercle bacilli from laryngeal swabs. Not less than 30,000 cultures have been prepared in the last two years from patients whose smears were microscopically negative. In 15 to 20 per cent the culture was found to be positive.

This ascitic fluid medium is not suitable for the surface growth of tubercle bacilli because of its low concentration of necessary chemicals. Ascitic fluid seems to act as an inhibitory factor in surface cultures. We used, therefore, in the following experiments on the influence of potassium tellurite on the surface growth of tubercle bacilli, Lockemann's nonprotein synthetic medium which has the following composition:

Monobasic sodium phosphate + 12H ₂ O.....	3.0 g.
Monobasic potassium phosphate.....	4.0 g.
Magnesium sulphate + 7H ₂ O.....	2.5 g.
Sodium citrate (neutral).....	2.5 g.
Ferric ammonium sulphate.....	0.01 g.
Asparagin.....	5.0 g.
Glycerin.....	25.0 cc.
Water q.s.ad.....	1,000 cc.

This solution is autoclaved at 120°C. for twenty minutes and poured in Erlenmeyer flasks, 125 cc. in each. The pH of the medium is 5.6, and it is not necessary to adjust it to 7.0.

As a laboratory strain of tubercle bacillus we have used E5, *typus humanus* from the State Institute in Copenhagen.²

For the reaction, 0.1 per cent aqueous solution of potassium tellurite (Coleman and Abel c.o.) was used.

In order to have the same concentration of potassium tellurite in all tubes with colonies of tubercle bacilli, distilled water is added to restore the amount of fluid lost during evaporation in the incubator; then, 1 cc. of 0.1 per cent of the reagent is added and the tubes are placed again in the incubator. The result of the reaction is recorded for the first time forty-eight hours and for the second

* For this strain we are indebted to Prof. K. A. Jensen from the Statens Serum Institut in Copenhagen.

time seventy-two hours after the addition of the reagent. A positive tellurite reaction, that is, the reduction of the colorless aqueous solution of potassium tellurite to tellurium, is shown by the brown-black discoloring of the colonies or of the growth membrane, corresponding to the concentration of potassium tellurite used for the reaction. A negative tellurite test is recorded when, after addition of the reagent, no color change occurs in the colonies or in the growth membrane.

TABLE 1
Relation of tellurite test to age of cultures

NUMBER OF CULTURE	AGE OF CULTURE	RESULT OF THE TELLURITE TEST AFTER			
		48 hours		72 hours	
		Centre of the colonies	Periphery of the colonies	Centre of the colonies	Periphery of the colonies
44105/45	3 weeks	++	+++	++	+++
3226/45	3 weeks	+++	+++	+++	+++
3157/45	3 weeks	++	+++	++	+++
3084/45	3 weeks	+++	+++	+++	+++
3027/45	3 weeks	+++	+++	+++	+++
2943/45	6 weeks	—	++	—	++
2872/45	6 weeks	+	+++	+	+++
2882/45	6 weeks	+	++	+	+++
2887/45	6 weeks	—	+	—	+
2935/45	6 weeks	—	—	—	—
9863/44	5 months	—	—	—	—
9737/44	5 months	—	—	—	—
9755/44	5 months	—	—	—	—
9828/44	5 months	—	—	—	—
10303/44	5 months	—	—	—	—

+++ = black discoloration of the colonies.

++ = brown discoloration of the colonies.

+ = light brown discoloration of the colonies.

— = no change in color.

EXPERIMENTAL OBSERVATIONS

In a series of experiments the relation between the age of the cultures and the tellurite test was studied. Table 1 gives the results of these experiments.

Table 1 shows that the same colony reduces differently the potassium tellurite; the marginal parts of the colony reduce potassium tellurite intensively, while the centre shows a negative tellurite test. After five months' storage in the incubator at 37.5°C. the cultures lost their ability to reduce potassium tellurite.

A series of experiments was carried out with bacilli killed by heat, ultraviolet rays, chemical disinfectants. All these experiments showed that dead tubercle bacilli always yield a negative tellurite test.

In another series of experiments the effect was tested that potassium tellurite

has on the surface and depth growth of the human strain E5 in Lockemann's synthetic medium to which different amounts of tellurite were added. The results are presented in tables 2 and 3.

TABLE 2

Effect of tellurite on surface growth of the human strain E5 in Lockemann's synthetic medium

AGE OF CULTURE IN WEEKS	CONTROL	CONCENTRATION OF POTASSIUM TELLURITE			
		1:5,000	1:10,000	1:25,000	1:100,000
1	—	—	—	—	—
2	+	—	—	—	+
4	+++	—	—	+	+++
6	++++	—	—	++	++++

— = no growth; +, ++ = thin surface growth; +++ = surface growth not quite covering the surface of the liquid; ++++ = profuse surface growth completely covering the surface.

TABLE 3 .

The depth growth in Lockemann's medium, inoculated with 0.01 mg. of strain E5 (moist weight)

AGE OF CULTURE IN WEEKS	CONTROL	CONCENTRATION OF POTASSIUM TELLURITE			
		1:5,000	1:10,000	1:25,000	1:100,000
1	—	—	—	—	—
2	+	—	—	—	—
4	+	—	—	—	—
6	++	—	—	—	—

— = no growth; +, ++ = growth.

DISCUSSION

From these experiments it appears that the results of the tellurite test change with the vitality and the age of the colonies, grown in the depth of ascites fluid medium. Freshly isolated primary cultures, colonies of tubercle bacilli not older than three weeks, react on the whole in accordance with the concentration of potassium tellurite, which is reduced equally in all parts of the colony (figure 2). Colonies older than one month show complete reduction of potassium tellurite in some parts, while others are unable to reduce it. There are, therefore, in the same colony two kinds of tubercle bacilli, one showing reduction, as shown by the black discoloring of a part of a colony, the other showing no reduction (no change of color) (figures 3 to 6). Usually the centre of the colony, that is, the oldest part, shows no reduction, while the marginal parts reduce potassium tellurite intensively. This behavior does not change a week after adding potassium tellurite to the medium nor after the use of a concentration ten times stronger. It was shown that dead tubercle bacilli never reduce

tellurite. Řetovský (5), in 1941, made similar observations on the reduction of TeO_4 and TeO_6 by corn grains and found that old or badly sprouting grains reduce TeO_4 in some parts only. He points out that there are certain relations between the positive tellurite reaction and the ability of the grain to grow. According to this author the tellurite reaction is a very important test for observing aging and dying of plant embryos. The same observation was made by Lakon. It may be expected that the tellurite test should differentiate precisely between dead and living microbes within a given colony. However, further experiments showed that evidence for such a contention is still incomplete. We have attempted to separate the parts of the colony giving a positive tellurite reaction from those giving a negative one and inoculated them separately into

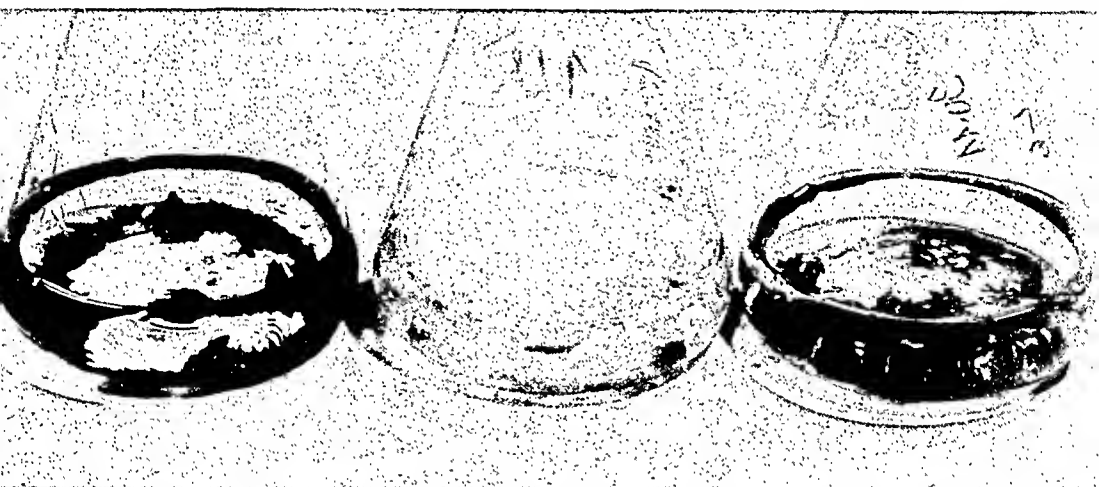


FIG. 1. The surface growth of *M. tuberculosis, typus humanus*, on synthetic Lockemann medium to which potassium tellurite in a concentration of 1:10,000 has been added. The middle flask serves as a control and contains the original medium. The growth on the tellurite medium is markedly impaired. The age of the culture is one month. (The membranes were originally on the surface of both media but moved to the ground during the transport to the camera.)

fluid and egg media. We have also tried to determine their virulence in guinea pigs. However, little difference in growth or virulence was found. This may be due to the difficulty of isolating completely the two parts of the colony. We still do not know why different parts of a colony of tubercle bacilli behave differently. It appears that the tellurite test serves as an index for the vitality of individual bacilli. Thus the most active bacilli, found at the periphery, give a positive test, while those in the central portions of the colony, being the oldest bacilli, give a negative tellurite reaction. It is possible, therefore, to use the tellurite test as an index for testing different physical and chemical factors in the vitality of tubercle bacilli. The growth membrane on Lockemann's medium, three weeks old, was exposed to direct sunlight for two hours. A part of the colony was covered with a filter absorbing the ultraviolet radiation. The

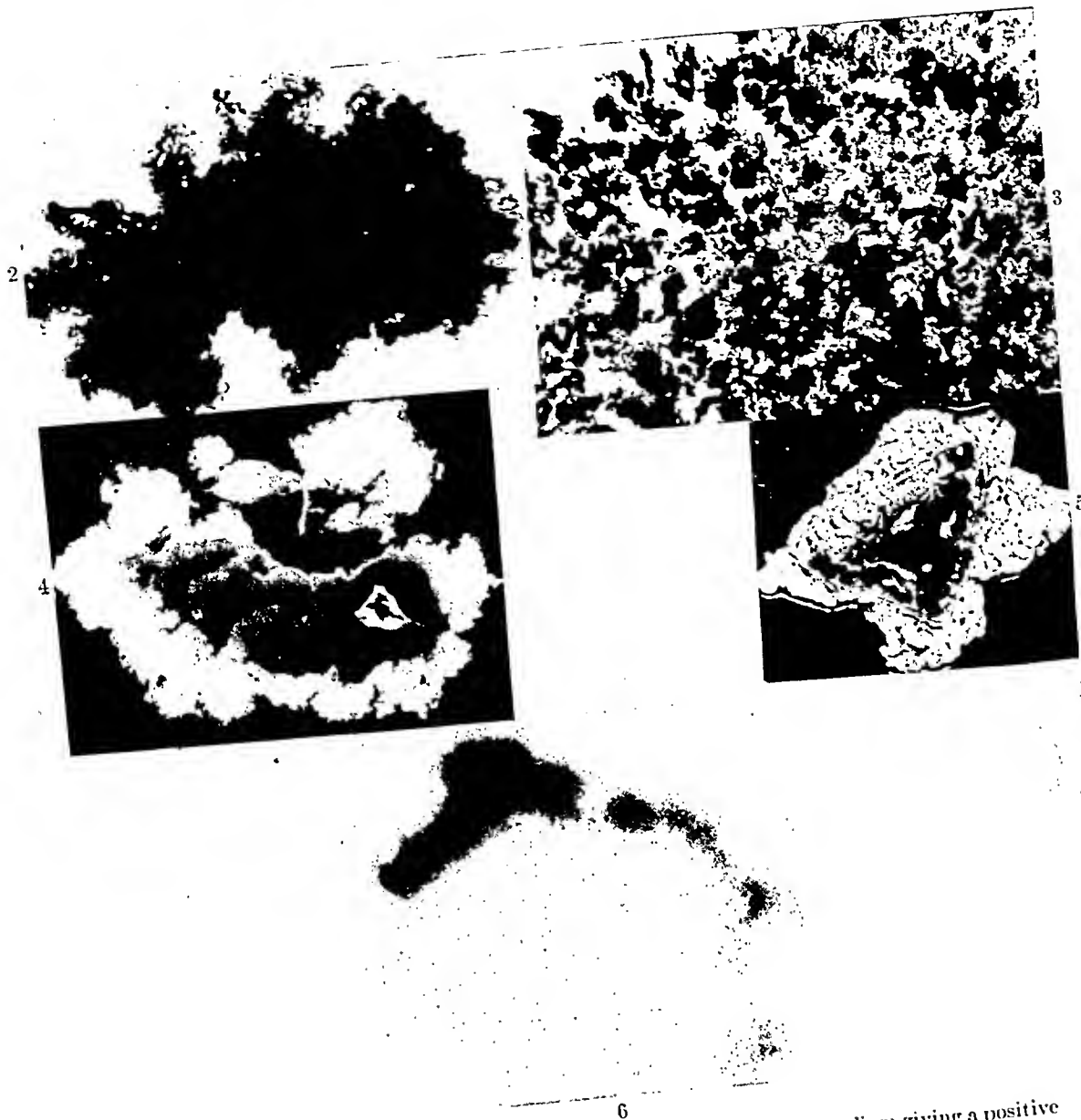


FIG. 2. (Upper left) Colony of tubercle bacilli from fluid ascites medium giving a positive tellurite reaction. The age of the culture is three weeks. The colony is equally discolored in all parts. The colony was spread between two slides and then photographed. (51 \times magnification)

FIG. 3. (Upper right) Colony of tubercle bacilli from fluid ascites medium. Age of the culture is two months. Areas with negative and positive tellurite test. (51 \times magnification)

FIG. 4. (Centre left) Colony of tubercle bacilli from fluid ascites medium. Potassium tellurite was added to three-weeks-old colony; forty-eight hours later the colony discolored by the reduced tellurium is transferred to a new ascites medium without tellurite. The peripheral part of the newly grown colony is colorless.

FIG. 5. (Centre right) Surface membrane of tubercle bacilli, three weeks old, exposed for two hours to sunlight. The tellurite test is negative in the periphery but positive in the central part which was protected from ultraviolet rays. (6 \times magnification)

FIG. 6. (Bottom) A colony of tubercle bacilli, two months old. The periphery of the colony shows a positive tellurite test, while the other parts show a negative one. (51 \times magnification)

tellurite test was positive only in the part covered with the filter. Further experiments were undertaken with different preparations of sulfonamides (Cibazol, sulfathiazole, albucid and prontosil). All these substances were not able to produce a negative tellurite test, even at a concentration of 25 per cent after forty-eight hours. This observation is in accordance with clinical findings.

The black color of the colony due to the reduced potassium tellurite is marked both in fluid and on egg medium. We have, therefore, attempted to produce an elective fluid medium with the potassium tellurite for primary isolation of tubercle bacilli. However, tubercle bacilli are very sensitive to potassium tellurite, and no depth growth occurs even in concentration of 1:100,000. But the surface growth is less impaired and in Lockemann's medium to which potassium tellurite is added growth is achieved even at a concentration of 1:10,000 (figure 1).

No explanation of the biochemical process which causes the reduction of potassium tellurite and of the entire redox system responsible for the reduction is so far available. Some observations suggest that the presence of SH groups is important for the reduction of potassium tellurite. This is indicated by the observation that the impairing effect of potassium tellurite is less obvious on the surface growth, which can be saturated with oxygen, than in depth growth, where the concentration of oxygen is low. In the depth growth the impairing effect of potassium tellurite is more marked probably because the SH groups as H acceptors are blocked by tellurite.

SUMMARY

The reduction of aqueous solution of potassium tellurite to tellurium by *M. tuberculosis*, shown by a black discoloration of its growth membrane or colonies, is described. This reaction is called the tellurite test. Fresh colonies of tubercle bacilli reduce potassium tellurite completely; old colonies show areas without tellurite reduction, especially in the centre of the colonies. A positive tellurite test indicates apparently the presence of living tubercle bacilli. A positive test obtained with a substance tested for tuberculocidal action gives clear proof of its ineffectiveness and no further tests are necessary to ascertain its bactericidal power. In primary depth culture in ascitic medium, potassium tellurite has strong inhibitory effect and abolishes growth even at a concentration of 1:100,000. On surface cultures in Lockemann's synthetic medium, tubercle bacilli grow at a concentration of 1:10,000, the growth membrane being completely black.

SUMARIO

La Reducción del Telurito Potásico por el Mycobacterium Tuberculosis

Describe la reducción de la solución acuosa de telurito potásico a telurio por el *M. tuberculosis*, traducida por una pigmentación negra de su membrana o colonias en desarrollo. Las colonias nuevas de bacilos tuberculosos reducen el telurito potásico completamente, las viejas revelan zonas de reacción negativa

para telurito, sobre todo en el centro de las colonias y en las zonas en cuya periferia es positiva la reacción para telurito. La observación de que los bacilos tuberculosos muertos dan una reacción negativa para telurito puede ser utilizada como técnica para estudiar el efecto de los agentes físicos y químicos sobre la vitalidad de los bacilos tuberculosos, pudiendo averiguarse el resultado al cabo de 24 a 48 horas, en tanto que otras técnicas exigen por lo menos 10 días.

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PULMONARY HEMATogenous TUBERCULOSIS IN THE ADULT¹

Anatomical Observations

DAVID M. SPAIN

Despite numerous anatomical studies on the pathogenesis of hematogenous tuberculosis in the adult, there still remain many controversial questions. Among these may be listed the determination of the most frequent site from which hematogenous dissemination occurs and the question of so-called isolated, non-miliary hematogenous tuberculosis of the lungs. This study is an attempt to add further information to the above and related problems.

METHODS AND CRITERIA

Six hundred and three consecutive necropsies on adults dying from tuberculosis were analyzed. Some of these necropsies were performed in a routine manner under the supervision of several pathologists. However, over two-thirds of them were performed by the author himself, and the histological material from the remaining third was also reviewed by the author. Nevertheless, the results obtained were compared with those from a similar group of cases that were meticulously studied by Medlar (1), and which the author had also observed. There were slight differences between the two groups of cases but these differences were quantitative rather than qualitative and in no way altered the basic conclusions of this report. Specific reference will be made to these observations.

The criteria for considering a case as one of hematogenous pulmonary tuberculosis were based on the accepted gross and histological standards. It was necessary for the lesions to be uniform in size and appearance, to be unrelated in their distribution to the general pattern of the bronchial tree, to be evenly distributed in both lungs and to be, not infrequently, in close proximity to the smaller branches of the pulmonary arterial system. In the terminal stage of cases it is very often difficult to decide whether the case is one of hematogenous tuberculosis of the lungs or not. Such cases may have been originally hematogenous in origin in the lungs but sooner or later a hematogenous tubercle may ulcerate into the bronchial tree and convert the process into one of mixed dissemination. This is particularly true of the subacute and chronic cases. Some of the cases with pulmonary cavities with or without laryngeal tuberculosis had a fine bronchogenic dissemination and it was difficult to distinguish these from cases with hematogenous dissemination. Such examples were not included in the hematogenous group. Only cases over the age of 15 were included.

DISSEMINATING SOURCES IN HEMATogenous TUBERCULOSIS

The question, that for many years has precipitated a lively controversy, is the one concerned with the sites and pathways whereby generalized tuberculosis develops. Painstaking studies have been performed in the past in attempts to solve this question. Yet it is interesting to note that equally competent observers have arrived at entirely different conclusions. Buhl (2) and Ponfick (3)

¹ From the Laboratories of Pathology and the Chest Division, (Columbia University, College of Physicians and Surgeons), Bellevue Hospital, New York, New York.

were representatives of the very large group that favored the lympho-hematogenous route, that is, spread from a caseous lymph node through the lymphatics into the thoracic duct and then into the general circulation. Weigert (4) and Pagel (5) were among the exponents of the view that the most common source for a generalized spread was from a caseous lymph node emptying directly into a venous channel. Weigert demonstrated tubercles in venous channels (Weigert's tubercle), originating from the tuberculous process in lymph nodes in over 50 per cent of the cases studied. Loeschke (6) and Wild (7) placed great emphasis on the possibility of hematogenous dissemination arising from such extrapulmonary foci as caseous lesions in the prostate, kidney and skeletal system. For some reason most investigators have constantly avoided implicating the caseous lesion within the lung parenchyma as being a direct source for a generalized hematogenous dissemination. The generally accepted opinion on this subject can best be illustrated by a quotation from Pinner's (8) excellent monograph on *Pulmonary Tuberculosis in the Adult*. This is from the section on hematogenous tuberculosis. "In many but not in all cases, the disseminating source can be identified on postmortem examination. The more common sources are: caseated lymph nodes of the primary complex (pulmonary and intestinal); a rupture taking place into a vein or less commonly into the thoracic duct; secondary caseated lymph nodes; caseous foci in the kidney, adrenal and prostate (particularly in older men), or in bones." Note the failure to include caseous foci in the lungs as a disseminating source for hematogenous tuberculosis. However, Pinner does note that "Weigert, in his classical paper on miliary tuberculosis, indicted caseous tubercles in the walls of pulmonary veins, foci that can frequently be demonstrated."

A contributing factor in the development of this concept has been the misconception held by some that generalized disseminated tuberculosis does not occur in the presence of chronic active pulmonary tuberculosis. This view was maintained by such prominent authorities as Schminke (9), Weigert (4) and Pagel (5). In the series reported here, however, over one-half of the cases of generalized tuberculosis were found in association with chronic tuberculous cavities in the lungs (table 1). Similar observations have been reported by both Orth (10) and Auerbach (11).

Study of the cases in this report supports the view that the caseous focus in the lung is not an unimportant disseminating source for hematogenous tuberculosis. In the adult the most frequent site for caseation necrosis is in the lung rather than in the lymph node. Careful examination of these caseous areas frequently discloses tuberculous phlebitis or less frequently caseous involvement of patent arterioles. It is not clear, therefore, why the caseous lesion in the lung should not be included as a potential disseminating source. In this series are included many cases that were carefully examined for the source of the hematogenous dissemination. In some of these, careful examination of all the lymph nodes and extrapulmonary sites failed to reveal any caseous foci that could be interpreted as being the disseminating site. On the other hand, caseous areas were found in the pulmonary parenchyma that involved and extended into

patent vascular channels, venous or arterial (see figures 1 and 2). An illustrative case of the embolic spread of caseous material directly from the pulmonary parenchyma was reported by Medlar (12). In his case there was an embolus of caseous material in a coronary artery. This had originated from tuberculous involvement of a pulmonary vein directly within the pulmonary parenchyma.

The greatest possible variation in the degree and type of lymph node involvement has also been found in this series of cases. Of the 100 cases with hematogenous pulmonary tuberculosis, 51 had cavities and 19 of these had caseous hilar lymph nodes; 39 had caseous lymph nodes without any significant chronic or active lesion in the lungs; in 10 cases the only chronic caseous foci were in extrapulmonary sites.

TABLE 1

Incidence of pulmonary cavities, caseous lymph nodes and extrapulmonary caseous foci in 100 cases of hematogenous pulmonary tuberculosis

AGE	CAVITY		CASEOUS LYMPH NODES		EXTRAPULMONARY FOCI	
	White	Negro	White	Negro	White	Negro
Under 20	—	—	4	3	—	—
20-29	5	5	—	5	1	—
30-39	5	7	—	6	3	1
40-49	6	5	5	5	1	—
50-59	4	4	3	1	1	—
Over 60	8	2	6	1	3	—
Total.....	28	23	18	21	9	1
	*†(51)		(39)		(10)	

* 19 of these cases also had caseous hilar lymph nodes.

† These are minimal figures as far as the lymph nodes are concerned since more careful examination would probably have revealed a few more with caseation necrosis.

As indicated previously, this series was compared with the one in which Medlar (1) meticulously studied 100 cases dying from tuberculosis. In 100 cases he found 17 had pulmonary miliary tuberculosis as part of a generalized dissemination. Eleven of these had caseous lymph nodes, 3 had completely calcified foci in the lymph nodes and 2 had no gross lesions in the lymph nodes. It is obvious, therefore, that in at least 5 of the 17 cases the generalized dissemination could not have originated in the lymph nodes. The fact that caseous involvement of the lymph nodes was present in 11 cases does not necessarily mean that these were in every instance the disseminating source, since, in some, caseous lesions were present also in the lungs. Thus, in 30 per cent of the cases described by Medlar and in approximately 40 per cent of the cases in this report, caseous lymph nodes were not found in association with hematogenous pulmonary tuberculosis. This finding is in disagreement with Auerbach's (11) statement that, "unlike the Weigert tubercle, vascular perforation or a thoracic duct focus, the caseous lymph node is always present when there is miliary dissemination."



FIG. 1. (Top) Section from active caseous focus in lung showing involvement of blood vessel. H. & E. $\times 134$
FIG. 2. (Bottom) Section from active caseous focus in lung showing involvement of blood vessel. H. & E. $\times 160$

Some specific examples are listed in order to illustrate the fact that every conceivable combination of tuberculous lesions might be present in association with generalized tuberculosis. Thus there was a case in which a caseous lymph node ulcerated directly into the left lower lobe branch of the pulmonary artery; a case in which a caseous lymph node ulcerated into the thoracic duct; others in which active caseous foci in the pulmonary parenchyma involved the vein in one instance and an artery in another instance; one in which there were no chronic lesions in the lungs or lymph nodes but in which there were chronic active caseous foci in the prostate that involved veins and arteries; one with a mass of caseous lymph nodes involving arterioles in the region of the cisterna chyli; and a case where there were tubercles in the thoracic duct associated with caseous hilar lymph nodes, probably indicating that the dissemination originated from the caseous hilar lymph node, with spread through the lymph vessels into the thoracic duct and thence into the general circulation. There were other combinations as well. These examples, however, serve to indicate that almost any conceivable combination of lesions and almost any type of dissemination may occur. The exact frequency of each type of dissemination was difficult to determine because often it was impossible definitely to identify the disseminating source. However, the impression was that the caseous lesions in the lungs were a definite and not infrequent source for the dissemination of hematogenous tuberculosis and that the caseous foci in the lymph nodes have been over-emphasized as the all-important disseminating source.

With regard to tuberculous prostatitis as a disseminating focus, age did not seem to be as important a factor as some observers believed (Pinner (8)). In the 8 cases in which it was thought that the caseous areas in the prostate were the disseminating sources, every age group from 15 on was represented. Amberson (13), relates a case in which an unrecognized tuberculous prostatitis was vigorously massaged. The patient shortly thereafter developed hematogenous tuberculosis. Tuberculosis of the prostate was subsequently discovered.

The divergent views regarding foci of dissemination reported by different observers may perhaps be explained by the fact that each investigator concentrated on uncovering a particular type of disseminating source without giving the same diligent care to the search for other potential foci. The possibility also exists that the hematogenous dissemination might take place simultaneously from several points rather than from one focus.

A comparison of the cases in which it was thought hematogenous dissemination originated from within the lungs as opposed to those in which it was thought that dissemination originated from caseous foci in the lymph nodes, revealed no significant differences as to the age, distribution and degree of involvement of the various organs. Whether or not there was any difference in the clinical course is not pertinent to this study.

AGE DISTRIBUTION OF HEMATOGENOUS TUBERCULOSIS IN THE ADULT

Closely related to the question of the source of dissemination is the incidence of generalized tuberculosis at different ages. It is well known that hematogenous

tuberculosis occurs far more frequently in infants and in children than at any other age period. In infants caseous lymph nodes are the dominant lesions. This fact was probably one of the more important ones responsible for the wide acceptance of the concept of lympho-hematogenous dissemination. For instance, in 50 consecutive necropsies on infants and children dying from tuberculosis, 49 had generalized spread with pulmonary miliary tuberculosis. There were no examples of isolated hematogenous pulmonary tuberculosis. Of the 50 cases, 47 had caseous lymph nodes, one had a calcified and caseous lymph node and 2 had fibrotic and calcified lymph nodes.

Histological sections of the pulmonary lesion in 30 of these cases were available for study. These were in most instances single sections taken at random through a representative portion of the lesion. Despite this fact, 14 of the 30 cases had

TABLE 2

Age distribution of 100 cases of hematogenous pulmonary tuberculosis with generalized dissemination

ALL CASES OF TUBERCULOSIS				HEMATOGENOUS TUBERCULOSIS		
Age	White	Negro	Total	White	Negro	Total
Under 20	5	3	8	4	3	7 (87%)
20-29	50	39	89	6	10	16 (18%)
30-39	109	49	158	8 (8.2%)	14	22 (14%)
40-49	124	32	156	12	10	22 (14%)
50-59	109	19	128	8	5	13 (10%)
Over 60	53	11	64	17 (36%)	3	20 (31%)
Total.....	450	153	603	55 (12.2%)	45 (29.4%)	100 (16.6%)

Note: Percentages are based on the total number of autopsies: 603.

tuberculous involvement of the blood vessels. Five of these had definite caseous tubercles in direct communication with the lumen in patent blood vessels filled with blood. This serves to indicate that in some of the cases, despite the presence of large caseous lymph nodes, a parenchymal lesion might just as well have been the focus for the generalized dissemination. It was also obvious that if more sections had been taken through these parenchymal lesions, considerably more vascular involvement undoubtedly would have been found.

The situation is not exactly the same in the adult. In the adult there is a steady decline in the incidence of hematogenous tuberculosis until the age of 60, when in the white male there is a marked increase. The number of cases in each age group in this series is too small to warrant any sweeping conclusions, but one cannot fail to be impressed with the fact that, in this series, the incidence of hematogenous tuberculosis in people dying from tuberculosis was four times as high in the white male over the age of 60 as in the white male between the ages of 20 and 60. Similar observations have been reported by Rich (14). (See tables 2 and 3.)

The reasons for this marked increase of the incidence of hematogenous tuber-

eulosis in the white male over the age of 60 are obscure. It was at least not accompanied by any significant increase of the incidence of caseous lymph nodes in this series. In Rich's (14) series, there was an increase of the incidence of caseous lymph nodes over the age of 60. Medlar (1), on the contrary, in a much larger series of cases noted a decrease of the incidence of caseous lymph nodes over the age of 60. However, the caseous lymph nodes when present and the hematogenous tuberculosis may be secondary manifestations of the lowered resistance from whatever cause rather than the one being the cause and the other the effect.

It is also worthy of note that, even in the age group over 60, every conceivable combination of lesions may be seen: that is, pulmonary cavities with or without caseous lymph nodes, with or without calcified lymph nodes; no cavity in the lung with or without calcified or caseous lymph nodes. If one attempts to classify the pathogenesis of these cases according to the accepted standards on

TABLE 3*

Frequency of military tuberculosis according to age groups and race

RACE	AGE	ALL CASES OF PULMONARY TUBERCULOSIS	MILITARY TUBERCULOSIS	ENLARGED CASEOUS NODES
White.....	25-50	71	3- 4%	1- 1.4%
White.....	60 and over	46	9-19.5%	3- 6.5%
Negro.....	25-50	86	14-16.3%	17-19.7%

* From Rich (14).

the basis of necropsy findings, some might be listed as recent primary infections, others might be called disseminations from reactivated dormant or latent caseous foci, and still others might even fall within the reinfection group. In any individual case, it is almost impossible to be sure of the exact pathogenesis. This makes it quite unlikely that the pathogenesis can be determined with any degree of certainty on purely clinical and roentgenographic evidence. The recent studies of Terplan (15), and those being conducted at present by Medlar (1) in which the incidental lesions of tuberculosis are being studied at necropsy in patients dying from other diseases than tuberculosis, are much more fruitful fields for the determination of the pathogenesis. However, even their studies may fall short of conclusive results because in all of their cases the exact time of the onset of the original infection was not known. Only by means of a long-range and comprehensive investigation of a stable community of people, in which tuberculin tests and X-ray studies are performed at stated intervals, beginning at birth and combined with necropsies on these individuals if they should die of some other disease than tuberculosis, can any real additions be made to the understanding of the exact pathogenesis.

ISOLATED HEMATOGENOUS PULMONARY TUBERCULOSIS

Of the 603 cases in this series, 100 were classified as examples of generalized dissemination with hematogenous pulmonary involvement; 131 cases had gener-

alized dissemination without any wide-spread hematogenous lesions in the lungs. Not a single case was classified as isolated hematogenous pulmonary tuberculosis. (See table 4.)

It will be noted that 16.6 per cent had hematogenous pulmonary tuberculosis and generalized dissemination, the incidence being higher in the Negro than in the white. Auerbach (11) recently reported an incidence of 17.5 per cent. Pinner (8a) commented: "There are not enough descriptive details to know the author's diagnostic criteria for miliary tuberculosis. This is pointed out, since the incidence (17.9 per cent of all tuberculosis deaths) is unusually high." Perhaps the incidence as reported by Auerbach, with which this report is in agreement, can be explained on the fact that a higher percentage of Negro patients and acute cases are admitted to the institutions from which both this and Auerbach's series were compiled than are admitted to some other institutions.

TABLE 4

The incidence of disseminated tuberculosis in adults dying from tuberculosis

	TOTAL	WHITE	NEGRO
All cases dying from tuberculosis.....	603	447	153
Cases of generalized dissemination with pulmonary involvement.....	100 (16.6%)	55 (12.3%)	45 (29%)
Cases of generalized dissemination without pulmonary involvement.....	131	—	—
Cases with isolated pulmonary hematogenous dissemination.....	—	—	—

Also, lower figures obtained by others may be due to information based on vital statistics, whereas our figures are based on necropsy statistics.

Despite the fact that in this series there was not a single case of hematogenous pulmonary tuberculosis without miliary tuberculosis in other organs, clinicians in the field of tuberculosis constantly refer to isolated pulmonary hematogenous tuberculosis. A review of the literature failed to reveal any careful documented evidence to support this contention. Reference is constantly made to the case of a physician who with suicidal intent inoculated himself intravenously with a virulent culture of tubercle bacilli. At postmortem examination, hematogenous lesions were found only in the lungs. This case, however, is hardly analogous to the natural development of hematogenous tuberculosis where at the time of the dissemination there are both an active caseous focus present in the body and an altered state of resistance and reactivity.

On the other hand, one of the cases observed by the author was that of a 76-year-old white male in whom a caseous lymph node eroded into the right lower lobe branch of the pulmonary artery. There was generalized involvement with miliary tubercles in all of the organs, including the lungs. In the right lower lobe the miliary tubercles were more numerous. In this case the tubercle bacilli were presumably carried into the right lower lobe first and produced miliary lesions. However, the majority of the tubercle bacilli were apparently carried through the capillary bed of the right lower lobe and then into

the general circulation and the other organs (kidneys, spleen, liver) became infected. There were still sufficient tubercle bacilli present on the return of the blood to the heart and then to the pulmonary artery to infect both lungs with the resultant wide-spread formation of miliary tubercles.

This type of case tends to militate against the view that, in a generalized dissemination, all tubercle bacilli can be filtered out in passing through the lungs, so that no infection results in the other organs. As a matter of fact, the presence of miliary tubercles in other organs without similar involvement of the lungs occurs more often than in combination with hematogenous tuberculosis of the lungs. (See table 1.)

Other examples that tend to contradict the view that isolated hematogenous pulmonary tuberculosis may occur are those cases in which caseous foci in the prostate were the disseminating sources. In them the tubercle bacilli usually entered the systemic venous circulation and were first carried into the lungs. Despite this, every one of these cases had miliary lesions in other organs, indicating that the lungs did not filter out a sufficient number of tubercle bacilli to prevent a generalized infection. In the case cited above and in some of the prostatic cases, there was an old tuberculous lesion present, so that even in these cases, despite the changed allergic state, the tubercle bacilli were not localized in the lungs.

NON-MILIARY HEMATOGENOUS TUBERCULOSIS OF LUNGS

An illustration of the view held by many clinicians regarding non-miliary hematogenous tuberculosis of the lung is contained in Pinner's (8b) monograph. "The lesions are fairly symmetrically distributed; and the upper third or half of the lung field is more frequently involved than the lower portions. Like all tuberculous lesions they may heal by resorption, fibrosis or calcification, but marked degrees of healing are probably more frequent than in bronchogenic phthisis of similar extent." Pinner (8c) admits that there is rarely strict scientific proof for this thesis and he further states, "But lack of scientifically acceptable proof is no argument against the clinical necessity of attempting the differential diagnosis of bronchogenic and hematogenous tuberculosis, particularly since significant group differences as to clinical course and prognosis are quite impressive."

On the other hand, anatomical evidence of the type presented above and of the case to be cited seems to indicate that the so-called non-miliary hematogenous tuberculosis of the type described by Pinner may actually in some of these cases be bronchogenic in development. The argument is offered that the failure to find anatomical evidence to support non-miliary hematogenous tuberculosis is based upon the fact that the usual end-stage anatomical picture has progressed too far and that an original hematogenous spread was later overshadowed by a bronchogenic dissemination. However, the author has had the opportunity of performing a necropsy on a case at a time when it could very well have been classified clinically as a so-called non-miliary hematogenous pulmonary tuberculosis. The case was that of a 17-year-old Negro male who by X-ray had bilateral nodular tuberculous infiltrations in the upper thirds of both lung fields.

A pneumothorax was performed and within forty-eight hours the patient died from an overwhelming streptococcus infection of the pleura. At necropsy bilateral round nodular caseous lesions were present in the lungs. These lesions, however, were directly related to bronchi and endobronchial tuberculosis was present. Caseous lymph nodes had ulcerated into the bronchi on both sides. In other words, postmortem examination, fortuitously performed at this stage of the disease, demonstrated that a case which clinically might have been classified as so-called non-miliary hematogenous tuberculosis was actually endobronchial in origin. It has been mentioned by Pagel (5) and supported by Pinner (8) that the so-called *Lochkaverne* (smooth-walled round cavity) is almost pathognomonic for hematogenous origin. In the case cited above, there were discrete caseous round infiltrates that in time might have shelled out, as they often do, and left behind a smooth-walled cavity. Thus, it is difficult to understand why a smooth-walled cavity should be interpreted as being pathognomonic of hematogenous lesions. In this series of cases it has not been possible to demonstrate any case that might be designated as an example of this so-called non-miliary hematogenous pulmonary tuberculosis.

It has also been impossible to make any distinction as to whether the hematogenous tuberculosis of the lung was due to dissemination through the pulmonary arterial system or the bronchial arterial system.

APICAL LOCALIZATION OF TUBERCULOSIS

The question as to why tuberculosis tends to become localized and develop best in the apex of the lung has given rise to various theories. Most of these have been concerned with the anatomical peculiarities of the lung as related to the apical portion of the thoracic cage, such as differences in circulation, lymphatics, bronchial drainage and expansibility. An interesting fact in connection with this has been pointed out in anatomical observations on the lesions in pulmonary miliary tuberculosis. It has been noted that after a period of time the lesions at the apex tend to become larger than in the remainder of the lung. There is an excellent illustration of this phenomenon in Rich's (16) text-book on *The Pathogenesis of Tuberculosis*. This finding was also observed on several occasions in this series. In addition, histological sections through the apical hematogenous lesions revealed a more pronounced cellular reaction with more caseation necrosis and a greater accumulation of peripheral exudate than were to be found about the lesions at the base of the lung. Not only was this difference observed when lesions in the apex and base were compared, but in a comparison of lesions in the lower portion of the lower lobe and the upper portion of the lower lobe.

Medlar (17, 18) has demonstrated that tuberculosis occurring naturally in cattle and tuberculosis produced experimentally by the intravenous inoculation of rabbits tends to localize and progress at the base of the lungs rather than the apex. However, as he pointed out, in these four-legged animals the base of the lungs actually represents the highest portion in the terms of posture and is comparable to the apex in the human being that is the highest portion of the

lung. Thus the reasons for localization in the apex of the lung in the human must be explained on conditions resulting from the erect posture rather than from the anatomical peculiarities of this part.

Dock (19), in a recent report, states that this localization of tuberculous lesions in adults is best explained "by the low level of pulmonary arterial pressure and the height of the column of blood from the right ventricle to apex when adults are erect. As a result the apex has little or no blood flow and the normal defense mechanism is inhibited through the normal waking hours." It is interesting to note that hematogenous tuberculosis of the lungs in infants does not result in the same differential development of the lesions as in the adult. The infant is not an upright animal. This would tend to confirm both Medlar's (17, 18) and some of Dock's (19) observations. It should be mentioned, however, that the author is unable to confirm Dock's observation that the combination of mitral stenosis and pulmonary tuberculosis occurs but rarely. The theory about low pulmonary arterial pressure also does not adequately explain the tendency for tuberculosis, as far as the lower lobe is concerned, to develop most readily in the apex of the lower lobe.

CONCLUSIONS

Anatomical evidence is presented to support the contention that caseous lesions of the lungs are an important source for dissemination in hematogenous pulmonary tuberculosis, while caseous lesions of the lymph nodes are not to be considered the all-important source for hematogenous tuberculosis.

In a series of 603 consecutive necropsies on patients dying from tuberculosis, generalized dissemination with hematogenous pulmonary tuberculosis was present 100 times.

Hematogenous tuberculosis limited to the lungs was not encountered. On the other hand, generalized dissemination without hematogenous pulmonary tuberculosis was present 131 times.

Hematogenous pulmonary tuberculosis with generalized dissemination occurred four times as frequently in white males over the age of 60 as in white males between the ages of 20 and 60. This was not associated with any notable increase of the incidence of caseous lymph nodes.

The differences in the development of miliary lesions in the apex and base of the lung are attributed to the upright posture of the human adult.

CONCLUSIONES

Tuberculosis Pulmonar Hematógena en el Adulto

Preséntanse datos anatómicos en apoyo del argumento de que las lesiones caseosas de los pulmones constituyen un importante foco de diseminación en la tuberculosis pulmonar hematógena, mientras que las lesiones caseosas de los ganglios linfáticos no deben ser consideradas como la causa más importante.

En una serie de 603 autopsias consecutivas en enfermos que murieron de tuberculosis, se encontró 100 veces diseminación generalizada con tuberculosis pulmonar hematógena.

No se descubrió tuberculosis hemat6gena limitada a los pulmones, y en cambio observ6se 131 veces diseminaci6n generalizada sin tuberculosis pulmonar hemat6gena.

La tuberculosis pulmonar hemat6gena con diseminaci6n generalizada fu6 cuatro veces m6s frecuente en los varones blancos de m6s de 60 a6os que en los de 20 a 60 a6os, sin que esto se asociara con mayor aumento de la incidencia de ganglios linf6ticos caseosos.

Las diferencias en la formaci6n de lesiones gran6licas entre el v6rtice y la base del pulm6n imput6nse a la posici6n erecta del hombre adulto.

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Edward R. Baldwin

1864-1947

By the death of Dr. Edward R. Baldwin, on May, 6 1947, one of the great figures in the antituberculosis movement in this country has passed from the stage.

His career will always be linked with that of Doctor Trudeau, whose work and ideals he shared so intimately and which he carried forward after Doctor Trudeau's death.

How this association began and what it signified is best expressed by Doctor Trudeau's own words in his autobiography:

"In December, 1892, a slender and pale young man rang my doorbell one morning and told me he was a doctor, had contracted tuberculosis, and wanted to go to the Sanitarium. Little did I know then how much the coming of this strange young man would mean to me personally, to my work, to Saranac Lake, and to the world at large! He told me his name was Edward R. Baldwin, that he was from New Haven; and when I asked what made him think he had tuberculosis, he quite floored me by his answer: that he had used his microscope and knew he had it. I admitted him to the Sanitarium.

"Through many long years of friendly fellowship, through many long years of work side by side, through many long years of physical misery and suffering my debt to Dr. Baldwin has steadily grown, until it has become a debt which I can never hope to repay but by affection and gratitude; a coin in which many debts, I find, are paid to him, because it is a coin he cannot possibly refuse to accept. Riches, fame and praise he scorns, but he cannot escape the heritage of affection and gratitude he so unconsciously and abundantly calls forth."

It is difficult to do complete justice to the many sided career of Doctor Baldwin which is so justly and succinctly epitomized in Doctor Trudeau's tribute. One can at best only feature the highlights and then perhaps venture an interpretation and appraisal.

While Doctor Baldwin practiced a good deal of clinical medicine, it was always a side issue to his interest in experimental research. His chief contributions in the clinical field were the position which he attained as adviser and court of appeal for the younger men in Saranac Lake and his profound influence upon both the clinical and ethical approach to their problems. He thus maintained the Trudeau tradition.

His interest in the laboratory began immediately after his arrival in Saranac Lake in 1892. He was soon made Director of the Saranac Laboratory which Doctor Trudeau had already set up, and this position he held until 1926. It was during these years that his main contributions to medical science were made. They were many and significant and are recorded in over one hundred published articles and in an authoritative book on the laboratory aspects of tuberculosis which he published with Doctors Petroff and Gardner, in 1927. His original investigative work centered around bacteriological, immunological and experimental features of tuberculosis. His experimental set-ups and his per-

formance were flawless; his interpretations and conclusions were logical and cautious; his self-criticism was steadily on guard and prevented premature reports and unjustified generalizations. At the turn of the century, when many highly reputed authors in Europe indulged in the early enthusiasm over tuberculin, antitoxins and other anti-*era*, both experimentally and therapeutically, Doctor Baldwin and his coworkers proved by careful experiments that all such current claims were not justified and that there was no foundation, in experi-



Edward R. Baldwin
1864-1947

ments, for any sort of "antitoxic" treatment. Whatever original and creative thought went into the planning of experiments, his published reports became famous for his logical, sound and meticulously accurate reporting of his studies. It was his boast that no published claim coming from his laboratory ever needed to be retracted and he was a hound on the trail of others which he proved to be unfounded, and because of his research and critical judgment many so-called "cures" were exposed. Thus he contributed to the avoidance of much disappointment and bitterness and to the saving of many lives.

Doctor Baldwin's position of leadership has been widely recognized. He was elected President of the American Clinical and Climatological Association in 1910; was President of the National Tuberculosis Association from 1915

to 1916; he was delegate to the League of Red Cross Societies at Cannes in 1919; he was Editor-in-Chief of the American Review of Tuberculosis from 1916 to 1921 and since that time until his death he was an active member of its Editorial Board, and since 1946 Editor Emeritus.

He was awarded the Trudeau Medal for outstanding contributions in the field of tuberculosis in 1927, and the Kober Medal for outstanding achievements in medicine in 1936. In 1937 the degree of Doctor of Science was conferred upon him by Dartmouth.

His contributions to the activities centering in Saranac Lake were particularly outstanding. During Doctor Trudeau's life, and more particularly after his death, Doctor Baldwin, as Chairman of the Executive Committee of the Trudeau Sanatorium and a member of its Board of Trustees, was the guiding hand in the notable work which that Institution has accomplished. In 1916 he was the chief instigator of the idea of establishing the Trudeau Foundation for carrying on research in tuberculosis and allied subjects, in collaboration with Dr. Walter B. James, and he has been largely responsible for the enviable position which this scientific Foundation has achieved in the field of research. Also in 1916 Doctor Baldwin conceived the idea of the teaching of tuberculosis to graduate students; he instituted the Trudeau School of which he became the Director. This School has done much to further the cause of postgraduate medical education in tuberculosis, and among the graduates is a number of scholars who have since become prominent in their own right. Doctor Baldwin's combined activities on behalf of the Trudeau Sanatorium, the Trudeau Foundation and the Trudeau School are achievements of the first magnitude.

At the same time that Doctor Baldwin was taking such a leading part in the medical activities at Saranac he was also greatly interested in the civic activities of the town. He was at various times President of the local Board of Health, of the Reception Hospital, of the General Hospital, was Chairman of the Boy Scouts and of the American Red Cross unit; he also was a Director of the Adirondack National Bank and a member of the State Health Commission.

Altogether it is not an exaggeration to state that for many years of his life Doctor Baldwin was Saranac Lake's first citizen.

After Doctor Baldwin's career as a physician, as a scientist and as a public spirited citizen has been reviewed, there still remain for consideration what are perhaps the most important factors of all in his life, namely his character and personality.

Reared in the atmosphere of a New England parsonage his early life was patterned by strict standards of discipline and good behavior rather than by demonstrations of sentiment or affection. This affected his demeanor throughout life and, to many, at first created an impression of coldness and lack of much human sympathy. Further experience, however, demonstrated to patients, friends and associates alike that beneath the surface there glowed a steady fire of deep understanding of human suffering and misfortune, although governed more by a sense of justice than by emotion. How deeply this was appreciated

by Doctor Trudeau, who knew him so well, is evidenced by the personal tribute which has been quoted.

Founded upon a background of deep religious conviction, Doctor Baldwin's life was characterized by a strong devotion to duty and to a sense of right as guiding principles. The standards of conduct which these engendered were as rigidly enforced upon himself as upon others. This gave him great power, the more obvious because maintained in spite of modern tendencies to the more easy moral standards which have prevailed in the world about him. Tempered though it was by his contacts with human suffering in his professional life, his attitude was uncompromising in its adherence to what he believed to be right and this had a profound influence upon all with whom he came in contact. Affection for him, therefore, was always mingled with the greatest respect for his character which was an outstanding attribute of his life, ranking even above his great scientific and professional attainments.

The memory of Doctor Baldwin's life will long be cherished by his host of friends and associates and the impression that he has made upon American medicine will always remain an important chapter in its history.

JAMES ALEXANDER MILLER

Doctor Baldwin's picture is a photographic reproduction of a portrait by Wilford S. Conrow.

Biographical Data

EDWARD H. BALDWIN

Born Bethel, Connecticut, September 8, 1864
 Son of Elijah Clark and Frances (Hutchinson) Baldwin
 Yale Medical School, 1890
 Intern Hartford Hospital, Hartford, Connecticut, 1890-1891
 General practice, Cromwell, Connecticut, 1891-1892
 Tuberculosis Specialist, Saranac Lake, New York, since 1892
 Married Mary Caroline Ives, June 1, 1895; one child, Henry
 Assistant and later Director of Saranac Laboratory, 1892-1928
 President, Saranac Lake Board of Health, 1898-1901
 President, Reception Hospital for Tuberculosis, 1901-1927
 President, 1912-1914, Saranac Lake General Hospital; member Board of Trustees 1912
 Editor-in-Chief, American Review of Tuberculosis, 1916-1921
 Member, Editorial Board, American Review of Tuberculosis, since 1921
 Vice-President, Trudeau Sanatorium, 1916-1934
 Chairman of Executive Committee, Trudeau Sanatorium, since 1916
 Honorary President, Trudeau Sanatorium, since 1945
 Instituted the Trudeau School of Tuberculosis, 1916
 Inaugurated (with the late Dr. Walter B. James) The Edward Livingston Trudeau Foundation, a \$500,000 endowment of tuberculosis research and teaching, 1916-1917
 Director, Trudeau Foundation and School, 1916-1938
 Contract Surgeon Tuberculosis Consulting Examination Board, Camp Devens, 1918
 Member U. S. delegation to Conference at Cannes, France, 1919, League of Red Cross Societies

President, 1910, and Emeritus Member, American Climatological and Clinical Association
 President, National Tuberculosis Association 1915 and 1916
 Member Saranac Lake School Board, Dist. 1, one year
 Member of the Medical Advisory Board, United States Veterans Bureau, 1930-1940
 Member, Consulting Medical Board, Adirondack Council, 1928-1932
 Chairman, Saranac Lake Committee Boy Scouts of America, Adirondack Council, 1928-1930
 Chairman, Saranac Lake Chapter, American Red Cross, since 1930
 Member, New York State Health Commission, Tuberculosis Committee, since 1931
 Director, Adirondack National Bank, since 1935
 Author of over 100 scientific papers on the subject of tuberculosis; in books the following chapters: Klebs' "Tuberculosis," *Resistance, Predisposition and Immunity*, 1909; "Osler System of Medicine," all three editions, *History and Etiology*; "Tuberculosis—Bacteriology, Pathology and Laboratory Diagnosis," with Doctors Petroff and Gardner, 1927
 Special laboratory experimental researches on infection, immunity and prevention of tuberculosis
 Member: Franklin County, New York State, and American Medical Associations
 American Climatological and Clinical Association (Emeritus)
 Association of American Physicians (Emeritus)
 National Tuberculosis Association (Life)
 American Association of Pathologists and Bacteriologists
 American Society for Clinical Investigation (Emeritus)
 New York Academy of Medicine
 Present positions: Honorary President, Trustee and Chairman of the Executive Committee, Trudeau Sanatorium
 Honorary President, Reception Hospital
 Chairman, Saranac Lake Chapter, American Red Cross
 Trustee, General Hospital of Saranac Lake
 Trustee, Saranac Laboratory
 Director, Adirondack National Bank & Trust Co.
 Member, Editorial Board, American Review of Tuberculosis
 Trustee, Northwood Sanatorium
 Honorary Degrees: Master of Arts, Yale, 1914
 Doctor of Science, Dartmouth, 1937
 Honorary Life Member, Tuberculosis Society of Scotland
 Awarded Trudeau Medal for outstanding work in tuberculosis, 1927
 Awarded Kober Medal, outstanding work in medicine, 1936
 Republican; Presbyterian
 Home: 6 Church Street, Saranac Lake, New York

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THE AMERICAN REVIEW OF TUBERCULOSIS¹

ABSTRACTS

VOLUME LVI

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ABST. No. 3

Bronchiectasis.—The literature on the pathogenesis of bronchiectasis is critically surveyed; the author concludes that the earlier assumed causes are "inconstant or controversial or unsatisfactory." Several reasons are enumerated against the assumption that elastic tension following atelectasis along with infection of the bronchial wall is the cause; but even if these forces are present their efficacy is doubtful because (1) dilatation may precede the destruction of the bronchial wall, (2) increased elastic tension is not selective for the atelectatic section of the lung, and infection is neither constant nor selective; bronchiectases are selective only as far as the atelectatic section is concerned, (3) lobectomy is followed by an increase of the elastic tension in the remaining lobes, but in spite of this, bronchiectasis does not develop in those lobes, (4) the bronchial dilation beyond an obstruction may fail to appear or may be slight in part of the collapsed section. The author assumes that there is only one cause for bronchiectasis which then must be common to the genesis of all cases. The metapneumonic atelectatic and "idiopathic" bronchiectases, (the author assumes that the origin of the latter may be also metapneumonic or atelectatic) have initially one important factor in common: the bronchi are imbedded in non-aerated tissues. The inspiratory movements of the chest wall and diaphragm tend to dilate bronchi, particularly if the latter are surrounded by atelectatic lung tissue. Clinical observations are supposed to confirm that this mechanism is the main or only genesis of bronchiectasis. Since early bronchial dilata-

tion is reversible, early diagnosis is important and bronchography is advised in every suspected case. Early treatment must aim at elimination of dilating forces, including pneumothorax if necessary.—*Genesis of Bronchiectasis, An Unappreciated Broncho-dilating Force*, B. Gladnikoff, *Acta med. Scandinav.*, 1946, 126: 411.—(O. Pinner)

Bronchogenic Carcinoma.—The operability of pulmonary carcinoma at the time of diagnosis remains disappointingly low. The author surveyed 343 cases observed at the University of Michigan Hospital from January, 1938 to January, 1944. This study is based on 231 patients in this group in whom diagnosis was verified histologically. Over 80 per cent of the cases were males. Age varied from 18 to 77, the majority occurring between 40 and 60 years of age. The majority of the lesions were close to the hilum; the remainder were of the peripheral type. The regional lymph nodes were the most frequent sites of metastasis. Next in order of frequency were the following: one or both lungs, pleura and liver, brain and one or more bones. The most frequent types of spread denoting inoperability were pleural involvement, supraclavicular nodes, recurrent laryngeal nerve paralysis, lesions at or adjacent to the carina, cerebral or bone metastasis, phrenic nerve paralysis and direct extension to the chest wall. Squamous cell tumors were found most frequently and offered the best prognosis. Prognosis was poorest in the undifferentiated cell-type. Adenocarcinoma was found most frequently in women. This latter prepon-

derance suggests a possible relationship between adenocarcinoma of the lung and bronchial adenoma which also occurs more frequently in females and has many histological similarities to adenocarcinoma. In over half the cases, the correct diagnosis was not made until nine or more months after onset of symptoms. The most frequent initial symptoms were cough, pneumonia, "flu", cold, chest pain, hemoptysis, dyspnea and ease of fatigue. Weight loss is usually a late manifestation. Early diagnosis depends on careful investigation of any prolonged respiratory complaints, particularly in males past 40 years of age. Bronchoscopy is the most important diagnostic procedure. The percentage of positive bronchoscopic biopsies was 90.1 in the inoperable group and 86.3 in the operable group. Aspiration biopsy is potentially dangerous and is not recommended. The presence of pleural fluid does not necessarily mean pleural metastasis but the presence of blood fluid generally denotes inoperability. Carcinoma cells were found in the fluid of 7 of the 38 cases with effusion. Tumor cells may sometimes be found in the sputum. If diagnosis cannot be otherwise established, exploratory thoracotomy is justified. Surgical extirpation is the only curative treatment. Pneumonectomy, rather than lobectomy, assures complete removal wherever this is at all possible. Except where employed for palliation in inoperable cases, X-ray therapy is condemned since any improvement in an operable case only postpones surgery. Only 77 cases were considered operable in this group and resection was possible in only 44. Seventeen, or 39.5 per cent, of the resected cases lived from two months to three years postoperatively. Thirteen, or 30 per cent, are alive two to seven years after operation. Empyema accounted for 4 of the 17 deaths following resection; present use of chemotherapy will probably reduce this incidence.—*Bronchiogenic Carcinoma: An Analysis of 348 Cases*, R. K. Hollingsworth, *Ann. Int. Med.*, March, 1947, 26: 377.—(H. R. Nayer)

Bronchial Adenoma.—After a review of the literature and presentation of 6 cases of bronchogenic adenoma the following conclusions are drawn: Adenoma of the bronchus represents a relatively simple diagnostic problem. It has been stated that this tumor is potentially malignant and that in most instances it degenerates into a bronchogenic carcinoma. By some continental observers it has been defined as carcinoid and by others as basal cell carcinoma. It also has been stated that, while clinically it is benign, pathologically it is malignant. The view that the adenoma is a benign tumor, by nearly all criteria, is gaining ground. Metastases have been observed in extremely few instances. They were few and minute and were discovered accidentally at postmortem examination. No recurrences were observed following removal of the tumor which *per se* caused no deaths. Not even locally is the adenoma malignant. In its growth it may form a bulge but hardly ever a break through. The assertion that bronchogenic adenoma often degenerates into bronchogenic carcinoma has not been confirmed. The adenoma is expansive but not invasive. It is the commonest benign bronchial tumor, comprising from 6 to 12 per cent of all bronchial neoplasms. It is prevalent in patients in the third and fourth decades and occurs oftener in women and more frequently on the right side. It occurs in bronchi accessible to inspection with the bronchoscope and presumably easily diagnosed. Therapy applied in the early stages eradicates the disease, while dilatoriness is fraught with dangerous complications, such as putrid abscess and bronchiectasis, pneumonitis and empyema.—*Bronchiogenic Adenoma: Benign Tumor of the Bronchus*, B. M. Fried, *Arch. Int. Med.*, March, 1947, 79: 291.—(G. C. Leiner)

Mediastinal Tumors.—Operations for mediastinal tumors have been done on 109 patients in the Army Thoracic Surgery Centers in the U. S. during the past three years. The number is relatively small because of the routine chest X-rays before acceptance for military service. The cases in this series were

found when symptoms developed (15 cases) or by routine X-ray examinations of personnel on active duty (94 cases). There were 94 benign tumors submitted to exploration; 89 were successfully removed and 5 'tumors' proved to be aneurysms. Fifteen tumors were malignant, of which only 3 could be removed. There was no mortality from the explorations. Lymphogranulomata have not been included except when erroneous diagnosis resulted in exploration. The most common benign tumors were bronchogenic cysts (23), dermoids and teratomata (14), primary nerve tumors (29) and pericardial cysts (10). The most common malignant neoplasms were teratomata (6), with Hodgkin's disease being found four times. The usual location of each type of tumor is described. The relative safety of exploratory thoracotomy recommends it for treatment, as well as for diagnosis.—*Mediastinal Tumors: Report of Cases Treated at Army Thoracic Surgery Centers in the United States, B. Blades, Ann. Surg., May, 1946, 123: 749.*—(W. H. Oatway, Jr.)

Eosinophilic Granuloma.—A 31-year-old man was seen who complained of headache in the left occipital region and of backache. Roentgenograms revealed bony defects in the left parietal bone and in the occipital bone, and areas of destruction in the left iliac and the pubic bones and in the body of the third lumbar vertebra; fine nodular infiltrations were seen in the upper halves of both lungs. The blood count showed eosinophilia. A diagnosis of eosinophilic granuloma of bone was made. A biopsy from the lesion in the left parietal bone revealed histiocytes, focal accumulation of eosinophils, lymphocytes, plasma cells, increase in connective tissue and proliferation of the endothelium. Following roentgen ray therapy there was evidence of healing of the bone and lung lesions. The pulmonary lesion is believed to be a visceral involvement as a part of the general picture of eosinophilic granuloma of bone. "If this is true, this is the first such case reported."—*Eosinophilic Granuloma of Bone: Report of a Case with Multiple Lesions of Bone and*

Pulmonary Infiltration, A. Weinstein, H. C. Francis & B. F. Sprofskin, Arch. Int. Med., February, 1947, 79: 176.—(G. C. Leiner)

Air Embolism.—In pulmonary (venous) air embolism, air enters one of the systemic veins, is carried to the right heart and obstructs the outflow tract of the right ventricle. In arterial embolism, air enters the pulmonary veins and is carried to the left heart and into the systemic arteries. The symptoms and signs of pulmonary air embolism are a loud, churning sound over the heart, rise of venous pressure, cyanosis, falling blood pressure, rapid pulse and syncope due to cerebral ischemia. In arterial embolism various neurological manifestations and symptoms and signs of myocardial infarction occur. Ten dogs received air injections into the femoral vein with the thorax intact. In 10 dogs the thorax was opened by a sternum-splitting incision before air was injected into the femoral vein. The following factors were found to be related to mortality: (1) Amount of air injected. (2) Speed of injection. (3) Position of animal: The animal can tolerate more air when lying on his left side than in any other position. (4) Effectiveness of the pulmonary excretory mechanism: Tachypnea tends to prevent death. Death was found to be caused by circulatory obstruction resulting from an air trap in the right ventricular outflow tract. Displacement of the air trap by turning the body in to the left lateral position may be life saving, even after the right ventricular contractions have become feeble. The electrocardiographic changes seen in air embolism are discussed.—*Pulmonary (Venous) Air Embolism, T. M. Durant, Joan Long & M. J. Oppenheimer, Am. Heart J., March, 1947, 33: 269.*—(G. C. Leiner)

Bronchial Obstruction and Emphysema.—When a bronchus is completely obstructed atelectasis results. If the obstruction is not complete, alveolar emphysema of the area ventilated through that bronchus follows. The authors have studied the mechanism of

its production, since they were not satisfied with the usual explanations of its occurrence. The generally accepted theory has been that the intensity of the inspiratory pressure is more than that of expiration, and that, because expiration is weaker than inspiration, it becomes prolonged and more difficult, especially when there is any obstruction in the bronchus. As a result, the residual air increases and the alveoli become overdistended. Temporary narrowing of the bronchi was produced by inhalation of a bronchoconstricting aerosol containing acetylcholine. This reduced the caliber of the tubes and resulted in dilatation of the alveoli and emphysema with increase of lung volume. By the use of Genaud's pneumograph (P. Genaud. *Protection contre les gaz de combat*, 1 vol., Vigot, ed., Paris. Article "Physiologie du masque.") variations in pulmonary volume were recorded. Inspiratory and expiratory pressures were determined by having the subject make forced inspirations and forced expirations through a tube connected with a mercurial manometer. The pneumograph apparatus was modified by the addition of a mask with a central opening over which there was a diaphragm so that records could be made separately during inspiration and expiration. Over two hundred persons with either temporary (functional) or permanent (pathological) pulmonary emphysema were studied. It was found that the maximum force of expiration was uniformly greater than the maximum inspiratory pressure. In a number of normal subjects the ratios were as follows, expressed in millimeters of mercury: 25 to 40, 23 to 35, 17 to 26, 16 to 24, etc. During inspiration the inspiratory pressure falls while the bronchial caliber is increasing, and the phenomena counteract each other. On the other hand during expiration, the bronchial pressure steadily diminishes while the caliber of the bronchial tubes becomes less and less, making expiration more difficult and less effective than inspiration. In normal breathing no harm is done, but when the bronchus is obstructed either temporarily or permanently, dilatation of the alveoli and emphysema re-

sult. Therapeutic inferences made were that the inhalation of a broncho-dilating aerosol (containing adrenalin) could open the air passages, and breathing exercises could help to develop the expiratory pressure or force, especially in patients with functional or temporary emphysema.—*Emphysème pulmonaire d'origine bronchique*, R. Tiffeneau & J. Z. Schreiner, *Poumon*, November-December, 1946, 2: 375.—(A. T. Laird)

Occlusion of Bronchus.—Foreign bodies of vegetable origin located in the bronchus cause a guarded prognosis. The sooner the removal is done, the better is the prognosis. These foreign bodies absorb fluid and eventually convert a partial obstruction of valvular type into a total obstruction. The longer endobronchial removal is delayed, the greater the danger that the foreign body breaks and that fragments of it are disseminated into bronchioli. A boy who had aspirated a bean, which broke during the extraction, is reported. In this case, complete obstruction at the bifurcation resulted from the attempt of extracting the bean and tracheotomy was life-saving.—*Oclusion de bronquio por poroto: Complicaciones en su extraccion*, R. Scgre, *Prensa méd. argent.*, November 15, 1946, 33: 2313.—(W. Swienty)

Asthma and Heart in Children.—Seventeen children with asthma of an average duration of 4.7 years were examined by various routine and special methods to determine heart size and function. It is concluded that uncomplicated bronchial asthma is not a factor in the production of heart disease.—*The Influence of Bronchial Asthma on the Heart in Childhood*, V. J. Derbes & T. Engelhardt, *Arch. Pediat.*, April, 1946, 63: 166.—(W. H. Oatway, Jr.)

Staphylococcal Empyema in Infants.—Forty-two cases of staphylococcal empyema were seen at the St. Louis Children's Hospital in the ten years before penicillin became available. The series comprised 22 per cent of the empyemata from all causes. Staphylo-

coecus infection tended to occur more often in infants than in young children, and was by far the most common type in those under six months of age. In 40.5 per cent it became a pyopneumothorax. The fatality was 26.2 per cent. General supportive measures and adequate surgical drainage are the best therapy. The sulfonamide drugs and specific antiserum were of limited value.—*Diagnosis and Management of Severe Infections in Infants and Children: A Review of Experiences since the Introduction of Sulfonamide Therapy. V. Staphylococcal Empyema: The Importance of Pyopneumothorax as a Complication*, G. B. Forbes, J. *Pediat.*, July, 1946, 29: 45.—(W. H. Oatway, Jr.)

Penicillin for Staphylococcus Empyema.—Prior to the use of penicillin, fatality from staphylococcal infection of the pleural space was reported to be between 22 and 100 per cent. Sulfonamides and surgery were the most effective methods in such series. Eight cases were treated in Strong Memorial Hospital before penicillin; the mortality was 25 per cent. Seven cases were treated since penicillin became available; one patient died on the second day of treatment (14 per cent). Penicillin was used intrapleurally and intramuscularly, combined with sulfonamides by mouth, aspirations and trocar drainage.—*Penicillin as an Aid in the Treatment of Primary Staphylococcus Pneumonia with Empyema*, W. S. Davis, Mary E. Hyman & F. D. Rühstaller, J. *Pediat.*, January, 1947, 30: 55.—(W. H. Oatway, Jr.)

Horizontal Fissure.—Adhesive pleuritis produces shrinkage of the upper lobe in its central free portion. This results in retraction of the horizontal fissure so that the fissure describes a convex curved line on the roentgenogram. This finding has prognostic significance in regard to the possibility of an adequate pneumothorax.—*The Significance of the Retracted and Curved Horizontal Fissure of the Lungs*, R. E. Dwork, Am. J. *Roentgenol.*, March, 1947, 57: 544.—(J. E. Farber)

Silicotic Vascular Disease.—The perivascular deposit of quartz in the early stages of silicosis produces a stenosing endangitis, perivascular fibrosis and partial destruction of the elastic lamina of the vascular wall. The latter changes, in cases of coincident tuberculosis, facilitate passage of bacilli into the circulation and their dissemination by the blood-stream. *Endangitis obliterans*, by reducing pulmonary circulation, diminishes the working capacity of the patient at a time when pulmonary fibrosis, as seen radiologically, is still in an initial stage. This explains the absence of correlation between extent of fibrosis as seen on the X-ray film and vital capacity and working capacity. Extent and intensity of vascular silicosis are more evident after inhalation of pure quartz.—*Die klinische Bedeutung der silikotischen Gefäss-Schädigung*, E. Uehlinger & R. Zollinger, *Bull. d. Schweiz. Akad. d. Med. Wissensch.*, 1946, 3: 176.—(B. Gerstl)

Funnel Chest.—Funnel chest, or *pectus excavatum* is not a rare condition. The malformation is almost always a developmental anomaly and may be hereditary. Trauma to the sternum may produce an angulated fracture with resultant funnel chest. The deformity may be of varying degrees, with a depth reaching, at times, up to 7 cm. or more. The heart is usually displaced to the left. This is characteristically shown in the posterior-anterior roentgen view and is readily mistaken for cardiac enlargement. On the lateral view the diagnosis is self-evident as the sternum protrudes backward and is well behind the anterior chest wall. The foregoing is of importance in interpreting miniature chest films where an erroneous interpretation of cardiac disease may be made. In the absence of scoliosis left pleural thickening, left sided atelectasis, right sided pleural effusion, tumors and other known conditions, a presumptive diagnosis of funnel chest can be made when the heart is displaced to the left, with the right cardiac border hidden by the vertebral column, and with an elevated rounded left lower

cardiac border. Electrocardiographic variations in this condition are minor and are probably due to a change in the position of the heart rather than to myocardial disease. Uncomplicated nontraumatic developmental funnel chest does not produce symptoms of a serious nature, probably due to the adequacy of the various compensatory mechanisms. Dyspnea, cough, paroxysms of suffocation, rapid heart action and chest pain have been reported. Most cases of developmental funnel chest need no treatment. Surgical elevation of the sternum may have to be performed in traumatic cases if untoward cardiac manifestations occur. The authors report 9 cases of funnel chest. One of these had bigeminal rhythm due to regularly recurring right ventricular extrasystoles. This was probably due to an irritable focus in the right ventricle resulting from the constant pressure of the deformed sternum in this region.—*The Roentgen and Cardiac Manifestations of Funnel Chest*, J. Teplick & E. H. Drake, *Am. J. Roentgenol.*, December, 1946, 56: 721.—(J. E. Farber)

Rib Fractures.—A review of 4,029 cases of chest injuries disclosed 855 cases with single or multiple rib fractures. The one-film two exposure technique is described to facilitate the identification of the fractures. Using this technique, approximately 3 per cent more X-ray films were positive for rib fracture than by the usual technique.—*Fractures of the Ribs*, F. Liberson, *Am. J. Roentgenol.*, March, 1947, 57: 349.—(J. E. Farber)

Histoplasmosis in Infant.—Histoplasmosis was demonstrated in a 7-month-old girl with anemia, leukopenia and hepatosplenomegaly, by bone marrow biopsy, histoplasmin skin test and positive cultures from blood, marrow, stool and duodenal contents. Necropsy showed wide-spread dissemination of intracellular yeast forms throughout the body. Culture on 7 per cent horse-blood-agar containing 20 units per cc. each of penicillin and streptomycin at 32° and 38° C. yielded abundant filamentous forms in which charac-

teristic tuberculate chlamydospores developed, from all body tissues and fluids tested except the bile and the cerebrospinal fluid.—*Histoplasmosis in Infancy: The Pathologic Picture as Seen in One Case*, L. A. Weed, A. M. Iams & H. M. Keith, *Arch. Path.*, February, 1947, 43: 155.—(E. Bogcn)

Double Fungus Infection.—A Negro boy died about three months after the onset of a subacute febrile illness. *Cryptococcus neoformans* (*Torula histolytica*) and *Histoplasma capsulatum* were both grown from the blood and from exudate, and were seen in sections of lesions found at autopsy. Mycological and animal inoculation studies are described.—*Systemic Infection with Cryptococcus neoformans (Torula histolytica) and Histoplasma capsulatum in the Same Patient*, G. B. Mider, F. D. Smith & W. E. Bray, *Arch. Path.*, January, 1947, 43: 102.—(E. Bogcn)

Surgery for Actinomycosis.—Fifteen per cent of patients with actinomycosis have involvement of the thorax. The infection usually is aspirated to the lungs from the mouth. The pneumonic process suppurates, producing fibrosis, 'burrowing' and sinuses. The intrapulmonary spread is often greater than indicated by X-ray appearances. Only the sulfonamides and penicillin have given encouraging results, and they often require surgical assistance. Two typical cases are reported. Intensive chemotherapy for more than a year had not prevented a steady progress of the lesions. Pneumonectomy was done in each before spread from the lung had occurred. (A lobectomy was insufficient in one case, and the diseased basal lung tissue had to be removed at a second operation.) Four grams of sulfadiazine and 200,000 U. of penicillin were instilled intrapleurally each day for ten to fourteen days after operation. Daily aspirations were necessary for ten days. The recoveries were uneventful; one patient is well at six months, the other at a year following surgery.—*Pulmonary Actinomycosis*, E. B. Kay, *Ann.*

Surg., September, 1946, 124: 585.—(W. H. Oatway, Jr.)

Pelvic Tumors with Hydrothorax.—A review of the records of the Mayo Clinic disclosed 9 examples of hydrothorax and ascites among 20,000 cases of surgically removed pelvic tumors. The chief complaint was abdominal enlargement and frequently dyspnea. Pain was infrequent. Some patients had an unproductive cough. Physical examinations revealed a pelvic tumor, ascites and hydrothorax. Laboratory data were not significant. The tumors removed consisted of 4 ovarian fibromata, one degenerating uterine fibromyoma, one ovarian fibromyoma, one uterine fibromyoma with pelvic inflammatory disease, one granulosa cell tumor of the ovary and one teratoma of the ovary. The hydrothorax was on the right side in 7 cases, on the left in one and bilateral in one. The fluid in all cases was clear and straw-colored. The fluid showed no evidence of tuberculosis or neoplasm. The end-result in all the cases was good. There were no recurrences of ascites or hydrothorax. The longest period of survival in a case thus far is twenty-seven years.—*Certain Pelvic Tumors Associated with Ascites and Hydrothorax, M. Calmenson, M. B. Dockerty & J. J. Bianco, Surg., Gynec. & Obst., February, 1947, 84: 181.*—(A. G. Cohen)

Gastric Cyst in Thorax.—Only 16 cases of gastric cyst in the mediastinum have been found in the literature. One case is reported in which the cyst communicated with the bronchi of the right lung, producing pneumonitis and hemoptyses. Pneumonectomy was attempted, but the patient expired during the operation. The cyst communicated with a cavity in the postero-medial lung base. It was composed of gastric mucosa, musculature and nerves, and ended 5 cm. below the diaphragm in a blind sac.—*Thoracic Gastric Cyst, A. R. Valle & M. L. White, Jr., Ann. Surg., March, 1946, 123: 577.*—(W. H. Oatway, Jr.)

Phrenic Injury.—Paralysis of the diaphragm due to a birth injury to the phrenic nerve may occur and may produce serious symptoms. The eighth case of that sort to be reported was diagnosed by fluoroscopy on the seventh day of life, after three days of symptoms. Brachial paralysis was not associated. The nerve was 'rested' by placing the infant on the involved side, by continuous use of oxygen, and by gavage feedings. Normal function occurred after six days of treatment.—*Right-Sided Transient Paralysis of the Diaphragm in the Newborn Infant, J. V. Greenbaum & F. G. Harper, J. Pediat., April, 1946, 28: 488.*—(W. H. Oatway, Jr.)

Myasthenia and Thymic Tumor.—In 17 of a series of 100 cases of myasthenia gravis, X-ray examination disclosed a tumor in the anterior mediastinum. Exploratory operation was performed and in all but one case microscopic examination showed a tumor originating in the thymus gland. Routine fluoroscopy and lateral X-ray films as well as standard films are recommended for all cases of myasthenia gravis for the demonstration of thymic tumors.—*Roentgenologic Findings in Myasthenia Gravis Associated with Thymic Tumor, C. A. Good, Am. J. Roentgenol., March, 1947, 57: 305.*—(J. E. Farber)

Sympathectomy.—This procedure may be subject to the following complications: extrapleural hemothorax, pneumothorax, pleural effusion, atelectasis and mediastinal emphysema. Extrapleural hemothorax is the most serious of these complications. X-ray examination and diagnosis of extrapleural fluid collections is discussed.—*Pulmonary Complications of Dorsal Sympathectomy, R. C. Pendergrass & F. F. Allbritten, Jr., Am. J. Roentgenol., February, 1947, 57: 205.*—(J. E. Farber)

Sarcoidosis.—A study of 42 cases of Boeck's sarcoidosis is presented. The majority of these patients had involvement of the mediastinal and peripheral lymph nodes. A differential diagnosis between sarcoidosis and

lymphomata is presented. Radiation therapy of sarcoidosis is also discussed. The authors believe that radiation therapy is indicated when symptoms are present.—*Boeck's Sarcoid (Sarcoidosis)*, A. Oppenheim & R. S. Pollack, *Am. J. Roentgenol.*, January, 1947, 57: 28.—(J. E. Farber)

Tuberculosis in Sugar Plantations.—Examination of school children and pre-school children in the northern rural part of the State of Rio de Janeiro, Brazil, showed tuberculosis disease and tuberculosis infection rates comparable to those in the Federal District of the country and far higher than those in the southern part of the neighboring State of Espírito Santo. Among possible causes are sugar mills with comparatively recent industrialization. Tuberculosis infection rates in a sugar mill district averaged 29.4 per cent in pre-school children, as compared to 37.3 per cent in a single isolated school, 43.8 per cent in a kindergarten and 60.5 per cent in a school group. The infection rate decreased slightly and the disease rate increased with the proximity to rural areas. In a school group less than six miles from an urban centre, skin tests were positive in 80.3 per cent, as compared to 64 per cent in a similar group in the city of Rio. The high tuberculosis rates show the need of BCG vaccination in anergic cases. More than 1,000 children were vaccinated as a result of this study.—*A tuberculose nas usinas de açúcar do Norte Fluminense*, M. A. Fleury da Silveira, *Clín. tisiol.*, July-September, 1946, 1: 237.—(A. A. Moll)

Minimal Tuberculosis.—Fifty-five patients with small unilateral, active, radiologically non-cavitating tuberculous lesions underwent treatment in an institution. Thirty-four patients had bed-rest alone; of these, 17 relapsed, including 2 who relapsed twice. Twenty-nine patients received collapse therapy (8 after relapse in group 1); among these, there were no relapses. The patients who relapsed had been in the institution for the least length of time and had returned to work earlier. One-half of the relapses occurred

within the first year after discharge. Most occurred during the years 1943 to 1945 as a result of the exigencies of the war. Relapses in the conservatively treated group took place despite the patients having been away from work for three to eighteen months.—*The Treatment of Minimal Tuberculous Chest Lesions*, R. Heller, *Tubercle*, March, 1947, 28: 49.—(A. G. Cohen)

Treatment of Noncavernous Tuberculosis.—Tuberculosis literature deals largely with treatment of patients showing cavities in their lungs; scant attention has been paid to that ever-increasing number of early diagnosed non-cavernous group of patients with unilateral or bilateral infiltrations, with or without bacilli in their sputum. Which cases should be treated with pneumothorax among this group without cavities? Reports from the Øresund Hospital in Copenhagen analyzing unilateral cases in which the extension of the lesion was less than one-half of one lung, including cases with small cavities (up to 2 cm. in diameter) revealed that 63 per cent of the pneumothorax treated patients with cavities recovered as against only 26 per cent recovering with conservative treatment. In the non-cavernous cases, the corresponding figures for recovery were 56 and 42 per cent for the two types of therapy. A comparable series is presented in this paper from the Skørping Sanatorium, dealing with 226 patients without cavities and followed for at least five years. Only 36 patients received pneumothorax treatment for widely different types of lesions, making any conclusions impossible as to the efficacy of treatment. Of the 190 patients treated conservatively, results are rather poor regarding recoveries: 40 per cent of unilateral bacillary cases, 34 per cent of bilateral bacillary cases, 59 per cent abacillary unilateral and 50 per cent abacillary bilateral. Even though this series is small and statistically inconclusive, it is published to emphasize the serious prognosis of non-cavernous tuberculosis in every case under conservative treatment—a fact which appears to be insufficiently recognized.—*On the Treatment and*

Prognosis of Pulmonary Tuberculosis without Cavitation, E. Strandgaard, Acta tuberc. Scandinar., 1946, 20: 183.—(P. Q. Edwards)

Tuberculosis and Right Heart Disease.—

The electrocardiogram is the only useful means of detecting right heart strain before it becomes manifest clinically as right heart failure. Of the 163 patients with advanced pulmonary tuberculosis who were investigated, 71 showed alterations consistent with a diagnosis of right heart strain. It was determined that measurement of the circulation time, venous pressure and water balance was of little value in diagnosing the condition, inasmuch as the majority of patients who were investigated showed normal values. Digitalization is of value in patients with right heart strain before signs of decompensation are evident. This treatment is usually applied before major surgery is considered, and digitalis is continued for some weeks following the operation. In some cases an improvement in the electrocardiographic abnormalities was observed following digitalis treatment. In this series, the glycosides rather than whole digitalis preparations were used.—*Die Herzschädigung bei Lungentuberkulose und ihre Behandlung mit Digitalisderivaten, H. Steinlin, Schweiz. med. Wchnschr., January 11, 1947, 77: 72.—(H. Marcus)*

Asthma and Tuberculosis.—Six case histories are given to illustrate coexistence of asthma and tuberculosis. That asthma may mask the progress of a tuberculous infection is of serious concern, in so far as the clinician may not realize that the symptoms attributed to asthma, such as transient fever, wheezing, night sweats and dyspnea, may in reality be due to an active tuberculous lesion. Several additional case histories, with serial chest films, are presented to indicate the type of tuberculous lesion in which asthmatic symptoms are most likely to occur: tuberculous tracheobronchitis, bronchostenosis and torsion of a bronchus. Because of the frequent appearance of asthma-like symptoms in tuberculosis, regular roentgenological examination

should be made in all patients with asthma to prevent missing the more serious diagnosis of coexisting tuberculosis.—*Asthma and Tuberculosis J. G. Gerrits, Acta tuberc. Scandinar., 1946, 20: 236.—(P. Q. Edwards)*

Calcium Therapy.—The experimental and clinical experience with calcium in limiting exudative and allergic reactions forms the rationale of calcium therapy in pulmonary tuberculosis. It is felt that exudative and allergic phenomena frequently contribute to the clinical picture, and calcium injections have, therefore, been employed routinely as adjuvant therapy in the author's institution. Since 1927, 400,000 ampules of 10 to 20 per cent solutions of injectable calcium preparations have been used without serious reactions. Of the total, 350,000 injections were given intramuscularly, and only 4 infections were seen; 3 of these could be attributed to breaks in the technique. Twenty per cent calcium solutions are always given intravenously, and no serious consequences have ever been encountered. It is felt that the drug has been of definite value in reducing the exudative phase of the disease and in preventing or limiting pleural effusions. This applies to spontaneous pleural effusions as well as to effusions resulting from thoracoscopy and pneumonolysis, or to effusions occurring extrapleurally from extrapleural pneumonolysis. Any effect of the therapy on the blood calcium level is discounted because blood calcium determinations have shown that the calcium level is usually normal in pulmonary tuberculosis. Nevertheless it is felt that calcium therapy is helpful in reducing the number of fatal hemorrhages. Only 2 cases of fatal hemorrhage have occurred in 5,000 cases.—*Praktische Erfahrungen mit der parenteralen Calciumtherapie bei der Behandlung der Lungentuberkulose, H. Stöcklin, Schweiz. med. Wchnschr., January 11, 1947, 77: 85.—(H. Marcus)*

Acid-base Balance in Tuberculosis.—Changes in acid-base balance are rarely observed in pulmonary tuberculosis, unless the disease is extensive and terminal. When

kidney function is not normal, however, changes can be produced with relative ease by administration of acid or alkali. This study is concerned with 5 patients whose kidney function precluded adjustments in the acid-base balance by alterations in the urine. Acidosis and alkalosis were produced experimentally by administration of suitable drugs, and the influence of this on the blood and on the ventilation was observed. It was found that the oxygen saturation of the blood was only insignificantly altered by the presence of acidosis and alkalosis, but the carbon dioxide content and its partial pressure were profoundly affected. In acidosis these values are substantially lowered, whereas they increase with alkalosis. Acidosis increases pulmonary ventilation, whereas alkalosis depresses it. This is purely a function of the blood pH and does not depend on the carbon dioxide content of the blood, as used to be thought. Of interest is a marked increase in the dead space with acidosis, and its decrease with alkalosis. Increase in the dead space is in itself a bar to efficient ventilation, so that the presence of acidosis creates a vicious cycle. The total results in the 5 patients indicated that with moderate degrees of acidosis and alkalosis compensation is possible, and a constant pH is maintained. When the chemical disturbances in the blood are more profound, the body does not sacrifice its respiratory function for the sake of maintaining a constant pH, and a new, though inefficient, equilibrium is established at a lower or higher pH. This phase is called the phase of decompensated acidosis or alkalosis, respectively.—*Lungenfunktion und Säure-Basen Gleichgewicht des Blutes*, P. H. Rossier & K. Wiesinger, *Schweiz. med. Wchnschr.*, January 11, 1947, 77: 55.—(H. Marcus)

Sarcoidosis and Millary Tuberculosis.—Sarcoidosis is of growing interest to the sanatorium physician because of its relative frequency in his practice. Possible relationship between sarcoidosis and tuberculosis has prompted a great deal of discussion, the present report adding one more case history

to support the belief that the two diseases are in some way varying aspects of the same pathogenetic agent. In this case, histological studies of autopsy specimens revealed transitions from proliferative lesions typical of sarcoidosis to lesions with necrosis and caseation, typically tuberculous in character, supporting the view that millary tuberculosis in this case was a consequence of the earlier sarcoidosis. The patient had been BCG vaccinated, producing a positive Mantoux reaction to 0.1 mg. of tuberculin eighteen months before the first sign of sarcoidosis, at which time his tuberculin test was negative to 1.0 mg. He remained negative throughout the course of his disease, during which the sarcoidosis progressed from the initial hilar adenopathy and subchronic uveitis, to granulomatous lesions in the nasal mucosa, tonsils, epipharynx and pharynx, peripheral lymph nodes throughout the body, millary densities in the lungs and finally death from millary tuberculosis.—*Lymphogranulomatosis benigna (Schaumann) Complicated by Millary Tuberculosis in a BCG Vaccinated Patient*, L. Ehrner, *Acta tuberc. Scandinav.*, 1946, 20: 188.—(P. Q. Edwards)

Tonsillogenic Millary Tuberculosis.—The disease started in the 4 cases reported with subacute tonsillitis only later diagnosed as tuberculous. The lesions ulcerated within a few weeks and spread to the oral and pharyngeal mucosa. The lymph nodes of the neck rapidly became involved, and tuberculous abscesses formed in 3 instances. All cases occurred in young soldiers and terminated in millary tuberculosis one and one-half to three months after onset of the disease. Two cases were autopsied and the findings suggested the tonsillary tuberculosis as the primary focus.—*Über tuberculöse tonsillogene Sepsis*, H. R. Gadolin, *Acta oto-laryng.*, 1946, 34: 495.—(B. Gerstl)

Spirography in Bilateral Collapse.—At the Miguel Pereira Hospital at Rio spirography has shown a definite advantage over spirometry in the selection of patients for bilateral

collapse. A metabolism apparatus is used rather than Knipping's spiograph. Five cases are reported to demonstrate the value of the method. Spirometry reveals only vital capacity but does not reveal the breathing reserve, although the latter may contraindicate operations. This was the case in 3 of 6 instances presented.—*A reserva respiratória na colapsoterapia bilateral*, R. Fernandes & S. Rubens Barboza, *Clin. fisiol.*, July-September, 1946, 1: 503.—(A. A. Moll)

Lung Volume.—When exercise or a decreased oxygen tension in the inspired air make special demands for increased oxygen consumption, increase in the rate and depth of respiration ensues. An increased minute volume results. A third mechanism for increasing oxygen intake during periods of stress is discussed in this paper, namely the increase of lung volume during exercise. It is estimated that lung volume can increase from 55 to 70 square meter by about one-third. Such a mechanism has been postulated in the past, but experimental proof was lacking. The author has conducted numerous experiments designed to measure lung volume. In one set of experiments the entire subject, except his head, was enclosed in a body-plethysmograph and the increase in lung volume during exercise was measured directly. The subject could also be connected with spirometers from which air of any desired oxygen concentration was breathed. These results confirm the increase of lung volume when oxygen under lowered pressure is breathed. In another type of experiment, a recording thoracometer is used; although this does not measure lung volume it gives an accurate graphic record of changes in the size of the thorax from which lung volume can be calculated. Animal experiments support the theory that under resting conditions certain areas of the lung are closed wholly or in part to gas exchange. This may affect whole lobules or only primary lobules, or territories supplied by certain bronchioli, and these areas become opened up when lung volume increases. Several interesting theories have been advanced as to the mechanism responsible for opening such incompletely ventilated portions of the lung. The smooth muscle which is abundantly distributed throughout the lung plays an important rôle. This muscle is not only distributed in circular fashion around bronchi and bronchioles, but it is also found in the alveolar septa, especially in the pillars between the alveoli. This smooth muscle acts in harmony with the skeletal muscles of respiration. When increased demands for oxygen cause greater effort on the part of the skeletal muscles, their increased tone becomes manifest by a larger basic thoracic circumference. The result is a decreased tone of the smooth muscle within the lung, and previously un-aerated areas are thus opened up. Conversely, with the subjection at rest and breathing oxygen under normal tension, decreased tone of the skeletal muscles, and a smaller basic thoracic circumference coexist with increased tone of the smooth muscle, and portions of the lung become closed off. Adrenergic stimuli are well known to relax smooth muscle within the lung, and we may assume that cholinergic and vagotropic influences cause increased tone of the pulmonary smooth muscle. Another theory that has been advanced concerns the concentration of carbon dioxide locally within the closed lobules. As a lobule is closed off, the carbon dioxide concentration increases steadily as oxygen is resorbed. At a certain critical concentration the smooth muscle relaxes and the lobule again becomes aerated. There is some experimental evidence to support this "local bronchomotoric reaction" of Engelhardt. The preceding considerations find important applications in the understanding of bronchial asthma and other asthmatic states. Because of an antagonism between the smooth and the skeletal muscles of respiration, the lung volume is increased at rest. Even so the oxygen concentration is below normal because smooth muscle spasm within the lung closes off large areas from proper ventilation. When a bronchodilator spray is applied, smooth muscle spasm ceases. The closed off areas

again become ventilated, and with proper synchronism between skeletal and smooth muscle lung volume actually decreases with exercise, rather than increases, to the benefit of the subject.—*The Regulation of the Lung Volume and Its Disturbances*, F. Verzar, Schweiz. med. Wchnschr., Sondernummer, September 16-21, 1946, 76: 982—(H. Marcus)

Pulmonary Function Tests.—The occasional patient with less than 50 per cent vital capacity in whom surgery was nevertheless carried out and who showed no dyspnea except after exercise, suggested that the vital capacity is not an accurate indicator of pulmonary function and that ability of the lung tissues to diffuse oxygen is a large factor in pulmonary function. Blood oxygen saturation changes occur only when clinical evidence of anoxia is likewise present; hence some other means of determining permeability of alveolar tissues seemed indicated. To estimate pulmonary function, two factors should be determined: ventilatory function and diffusion function. The former is the resting minute volume of ventilation, and the maximum breathing capacity for one minute. Ventilatory reserve is maximum breathing capacity divided by minute volume, which is about 20 in normal males, and 13 in normal females. (Normal figures given by Cournard, Richards and Darlington: resting minute ventilation: 7.5 liters, maximum breathing capacity in males: 154 liters, females: 100 liters.) Oxygen diffusion is measured by the twenty-second use of a rebreathing bag containing a liter of air. Mean values for 23 normal males after a standard exercise test were 7.95 volumes per cent (± 0.851), for 25 normal females 8.30 (± 0.74). By this method, an oxygen volume per cent up to 9.5 was considered a good diffusion, above 10 was an indication of impairment of permeability and diffusion which would suggest caution in contemplation of major thoracic surgery. As a rule, there is no constant relationship between oxygen diffusion and ventilatory reserve; both factors should be ascertained and considered seriously before surgery. Tidal air bears no relation-

ship to ventilatory reserve or the diffusion of oxygen. Measurements of alveolar air are most unreliable as an indication of oxygen diffusion because of the unstable conditions in the alveoli. A study of 41 patients is presented in this paper, analyzing the estimations of pulmonary function by use of both ventilatory reserve and diffusion of oxygen. Eight complete case histories are given, with data on pulmonary function both before and after major thoracic surgery.—*The Value of Pulmonary Function Tests in Thoracic Surgery for Pulmonary Tuberculosis*, G. G. Ornstein, Quart. Bull. Sea View Hosp., October, 1946, 8: 279.—(P. Q. Edwards)

Oxygen and Carbon Dioxide Diffusion.—Equipment to measure the diffusion of oxygen in the alveoli consists of a rebreathing bag and a simplified oxygen and carbon dioxide analyzer. The analyzer which has an accuracy of ± 0.1 per cent is far easier to operate than the more accurate Henderson-Haldane apparatus. A detailed description of this analyzer is given. After a standard exercise test, subjects are connected for twenty seconds with a rebreathing bag containing one liter of air. In 22 normal adult males, the oxygen volumes per cent of 20.93 originally in the bag was reduced to a mean volume of 7.95 ± 0.851 ; carbon dioxide of 0.03 volumes per cent was increased to 8.09 ± 0.436 . In 25 normal females, the mean oxygen volume per cent was 8.30 ± 0.714 ; carbon dioxide volume per cent was 7.70 ± 0.497 . An oxygen volume per cent up to 9.5 is considered good diffusion of oxygen; above 10 is an indication of impairment of permeability and diffusion.—*Simplified Equipment for Estimating the Diffusion of Oxygen and Carbon Dioxide in the Lungs*, G. G. Ornstein, Quart. Bull. Sea View Hosp., October, 1946, 8: 303.—(P. Q. Edwards)

Phrenicectomy.—Of all operations on the phrenic nerve, phrenicectomy is the only one furnishing the long, continued rest required for the healing of cavities. Patients must be selected with care. Among some 800 chest

operations performed in a two-year period at the Miguel Pereira Hospital at Rio, only 25 were phrenicectomies, and in 3 cases these were associated with a pneumothorax. In 18 cases the operation was on the right side, and in 7 on the left. The age ranged from 12 to more than 50 years in 2 cases. The clinical type of the disease was ulcero-fibro-caseous in 10, ulcero-caseous in 10 and ulcero-fibrotic in 5. No statement can be made as to remote results since all patients are still under observation and a number of them were operated less than a year ago. The operation was at first limited to basal cases, but it is now being extended to lesions higher up.—*Limites e indicações da frenicectomia*, R. Fernandes, J. M. Castello Branco, J. Batista Rocha & J. Martins dos Santos, *Clin. tisiol.*, July-September, 1946, 1: 185.—(A. A. Moll)

Results of Thoracoplasty.—This is a review of 200 patients who underwent thoracoplasty for different types of tuberculosis. In this consecutive series, 188 patients were female and 12 were male. All together, 364 (or 1.8 stage per patient) stages were performed. Bilateral lesions were encountered in 98 cases. All patients had cavities. The majority, 77.5 per cent, were between the ages of 20 and 39, 11 per cent between 15 and 19, and one case was over 60 years. The indications for thoracoplasty depend upon the character of the lesions. Primary thoracoplasty should be done for apical cavities with fibrotic wall. All active lesions are perfect indications for thoracoplasty, provided that they are localized in the upper half of the lung field. Giant cavities give poor results, unless cavernostomy and phrenic exeresis are done previously. In minimal apical lesions, one stage is generally sufficient to control the disease, but lobectomy is preferable, provided the respiratory capacity is adequate. Giant cavities with a ball valve mechanism and retention of secretion as well as bronchiectasis are formal contraindications. The social status of the patient should not be neglected. If prolonged conservative treatment is not feasible, thoracoplasty should be done early. The operative risks are directly

related to the extent of the lesion. Patients under 15 and over 50 years give poorer results than those between 15 and 50. Pre- and post-operative care are as important for final satisfactory results as the surgical procedure itself. A complete cardiac and respiratory examination, including electrocardiogram and bronchoscopy, should be routine preoperative procedure. The author describes a modification of the classical thoracoplasty which he has used in one-fourth of his series. Subperiosteal resection of the third rib is followed by a total resection of the second and first ribs in their entire length, including the periosteum and the fixation of the second intercostal muscle to the paravertebral muscles through a hole in the third intercostal space. This procedure prevents regeneration of the two upper ribs and permits a postponement of the second stage until complete postoperative recovery has taken place and so lowers the mortality rate. In 150 consecutive cases in which the classical technique was used, 283 stages (1.9 stage per patient) were necessary, whereas in 50 consecutive cases with the new technique, only 81 stages (1.6 per patient) had to be done. Moderate apicolysis was done in all cases but in those with giant cavities. Postoperatively, six months of rest was considered minimal requirement. The results were: conversion of sputum to negative and apparent stabilization of the disease in 139 (69.5 per cent). Thirty-three patients, or 16.5 per cent, died. The others were improved or were lost sight of. The mortality in the unilateral cases was 14 (13.7 per cent), in the bilateral cases 19 (19.4 per cent). Four cases (2 per cent) had minimal lesions and all were cured. Fifty cases (25 per cent) were moderately advanced. Of those, 46 (92 per cent) were cured and 1 (2 per cent) died. There is a distinctive increase in mortality during the second and third stage and especially after revision-thoracoplasty. After the first stage, there were 10 deaths among 200 operations; 8 were operative and 2 late deaths. In the second stage, there were 18 (12.1 per cent) deaths among 148 operations, of which 12 were immediate and 6 late. After the

third stage or revision, there were 5 (31.2 per cent) deaths in 16 cases. The deaths have considerably decreased since aspiration-bronchoscopy and blood transfusions during the operation have been routinely employed. The author's modified technique shows a definite superiority over the standard technique. There were only 3 (6 per cent) deaths in his series of 50 with 84 per cent of conversion of sputum, whereas in the series of 150 operated on by the old technique, only 64 per cent were stabilized and 30 (20 per cent) died.—*Estado actual de la toracoplastia en el tratamiento de la tuberculosis pulmonar*, J. L. Gomez Pimienta, *Rev. méd. d. Hosp. gen. Mexico*, January, 1946, 8: 303.—(W. Swienty)

Resection for Pulmonary Tuberculosis.—The author relates his experiences of twelve months' work with Overholt in Boston. Lobectomy or pneumonectomy have decided advantages over thoracoplasty in selected cases of tuberculosis. There is immediate conversion of sputum and complete extirpation of the focus. The rapid cure means great economic advantage to society. Disadvantages are: the high mortality (which has decreased in the last 100 consecutive cases to only 3 per cent); the postoperative complications (6 per cent spread and 3 per cent broncho-pleural fustulae) and the reduction of lung function by emphysema. This can be remedied by subsequent thoracoplasty and phrenicectomy. Definite indications for radical surgery are limited to: residual cavities after thoracoplasty; tuberculoma; basal tuberculosis; insufflated cavities limited to one lobe and uncontrollable hemoptysis. For all other types, radical surgery for tuberculosis is still in its experimental stage.—*La cirugía radical en el tratamiento de la tuberculosis pulmonar*, F. E. Tricerri, *An. de cir.*, September, 1946, 11: 210.—(W. Swienty)

Pneumonectomy.—There is a place for pulmonary resection in the treatment of pulmonary tuberculosis, not in competition with established relaxation measures, but in a well defined group of patients without reason-

able hope of cure by collapse therapy. Most authors agree on the following indications for resection: (1) extensive bronchial stenosis, (2) tuberculoma, (3) cavities failing to close under adequate thoracoplasty, (4) lower lobe cavities not amenable to collapse treatment, (5) tuberculous bronchiectasis. A series in which lobectomy was performed in preference to thoracoplasty despite the possibility of performing thoracoplasty, yielded results two to four years postoperatively that compare unfavorably with those obtained by thoracoplasty in similarly suitable cases, both in terms of mortality rate and sputum conversion. The hazards of resection are due to: (1) the fact that tuberculosis is not limited to the parenchymal tissue of one lobe alone nor, in the majority of instances, even to one lung; (2) overdistension occurs in remaining lobes with reactivation of apparently healthy tissue in which there was quiescent or inactive disease; (3) bronchogenic spread occurs in a relatively high percentage of patients; (4) tuberculous empyema, either pure or mixed, is a frequent complication. A series of 18 patients is presented in which pneumonectomy was performed in 4 and lobectomy in 10 for one or more of the above indications. In 4 additional cases tuberculosis was not present or went unrecognized at the time of operation. Seven died, 7 are still living with active tuberculosis, and 4 have no complications to date. Tuberculous empyema occurred in 5 of the 7 dead, three to six weeks postoperatively. Tuberculous pericarditis caused death in one patient in whom a contralateral lesion was improving one year postoperatively. Circulatory failure occurred on the third postoperative day in the remaining death, but a contralateral spread was seen at autopsy. Exacerbation or spread of pulmonary tuberculosis was a factor in 4 of the 7 deaths and late extension to the pericardium was seen in another. Overdistension of the remaining lung tissue was apparently responsible for reactivation of tuberculous lesions in 4 patients including one of the fatal cases. Of the 7 remaining alive, one will probably die; the others seem to be doing satisfactorily. While

it is possible that removal of grossly involved lung tissue (eliminating toxemia) may help other lesions, overdilatation of the remaining lung is hazardous and Overholt's suggestion to tailor the chest to fit the lung is not always immediately practical. Two case histories are presented in detail.—*Lobectomy and Pneumonectomy in Pulmonary Tuberculosis*, D. Carr & J. S. Harter, *Dis. of Chest*, September-October, 1946, 12: 387.—(K. R. Boucot)

Cavernostomy.—Cavernostomy has been used sporadically for many years. Its present status is highly equivocal since the procedure is employed in such small, different series of cases. A review of 15 cavernostomies with apparently favorable results in 8 patients is presented. Indications are varied; a large cavity in a lung not suitable for thoracoplasty or resection was the most common situation in which cavernostomy was performed. After localization of the cavity by X-ray markers or lipiodol and methylene blue injection into the periosteum overlying the cavity, an incision was made for a 2 inch subperiosteal resection of the rib. Iodoform packing was used whenever free pleura was encountered and incision of the cavity was a second-stage procedure. Otherwise, the cavity was unroofed by removing the required number of rib segments to afford free drainage. High postoperative temperatures, possible because of autotuberculinization, for one to two weeks were usually seen. Tubercle bacilli disappeared from the wound secretions usually within the first week; sputum conversions, when obtained, became apparent in the first six weeks. Operative mortality was 2 out of 15.—*Cavernostomy*, L. A. Hochberg, I. Fink & W. M. Chardack, *Quart. Bull. Sea View Hosp.*, October, 1946, 8: 343.—(P. Q. Edwards)

Pleurisy with Effusion.—Pleurisy with effusion when cause is in doubt is believed to be tuberculous. It is sometimes followed by frank tuberculosis in the lungs or other organs. Present study is based on 233 patients who had pleurisy with effusion, from the Ealing Chest Clinic, 1937-1944. Forty-three had

X-ray evidence of parenchymal pulmonary tuberculosis and were excluded. The remaining 190 were kept under constant observation in the clinic for maximum periods up to the end of 1945, with the exceptions that one patient was lost after two and one-half years, and 8 ceased to attend, of whom all are known to be alive and well and at work. Of the 190, 40 have developed secondary tuberculosis, and 6 have died. The relative incidence of secondary tuberculosis was approximately the same in each age group. The case fatality rates were also evenly distributed. Of the 40 patients, 18 were male, 22 female. Approximately half of the cases of pulmonary tuberculosis developed within the first year after the initial pleurisy. No cases occurred after five years. Of the tuberculous lesions which developed, 15 per cent were extrapulmonary. The death rate for the five-year period was 3.5 per cent.—*Prognosis of Primary Pleurisy with Effusion*, B. C. Thompson, *Brit. M. J.*, April 12, 1947, 4501: 487.—(R. W. Clarke)

Renal Tuberculosis and Primary Infection.—Using erythema nodosum as the timing point for primary infection, it has been shown by others that tuberculous meningitis occurs most often within two months, pleuritis within six months, bone and joint involvement within two years and pulmonary involvement within five years. Genito-urinary tuberculosis seems to be an exception to this rule. An analysis of 292 cases of renal tuberculosis showed 55.8 per cent to be in men; 18 per cent showed bilateral involvement at the first examination. The time interval from erythema nodosum and pleuritis to the appearance of renal tuberculosis was less than one year in 5 cases, up to five years in 18 cases and more than fifteen years in 17 cases. There were also long intervals between other manifestations of tuberculosis and renal involvement: in 55 cases the interval was more than five years and in 21 it was more than fifteen years. One-half of the patients who had another manifestation of tuberculosis before the renal had more than one (up to 4 or 5) such manifestation. In this group there was involvement of the pleura in

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21 per cent, of the bones and joints in 22 per cent and of the lungs in 25 per cent. This discrepancy between the rapidity of onset in renal tuberculosis as compared to other manifestations of the disease may be explained in part by the slow evolution. In 44.8 per cent there was an interval of more than one year and in 25 cases more than five years between the first appearance of symptoms and the establishment of the diagnosis. It is likely that both kidneys are involved by hematogenous spread soon after the primary infection. There is then a very slow evolution of the disease.—*The Relation between Renal Tuberculosis and Primary Infection*, H. J. Ustvedt, *Tubercle*, February, 1947, 28: 22.—(A. G. Cohen)

Urogenital Tuberculosis.—A pavilion of 6 beds restricted to the care of male patients with urogenital tuberculosis has been opened at the sanatorium at Petit-Arbois, near Marseilles, to receive patients from all over France. Old stabilized ulcero-caseous unilateral renal tuberculosis will receive immediate surgical treatment, but patients will be prepared by several months of sanatorium care if the lesions are fresh and unstable. Further sanatorium care will be given after operation to enable fistulas to close, bladder residuals to heal, and to avoid the appearance of other tuberculous localizations. A few instances of light unilateral renal involvement with bacilluria but without open ulceration may heal on medical care alone. Specialized sanatorium care may also prolong the life and improve the general health of patients with bilateral renal tuberculosis. Since tuberculous epididymitis is only the visible evidence of more extensive bladder and prostatic involvement, its removal is chiefly a cosmetic procedure which should be preceded and followed by adequate sanatorium care.—*Lutte contre la tuberculose urogénitale*, B. Fey, *Presse méd.*, March 22, 1947, 55: 210.—(E. Bogen)

Genital Tuberculosis.—A case of atresia of the vagina in a 19-year-old, single, Negro woman, is presented. Because of anticipated

marriage, she wished to have a normal vagina constructed. There had been amenorrhea and a malodorous discharge for many years; otherwise she had been in good health. A Wharton technique was done and a diagnosis of chronic granulomatous endocervicitis, probably tuberculous, was made. X-ray films of chest and abdomen were normal, likewise were intravenous pyelograms. In view of the probable tuberculosis of the tubes as well as the uterus, four days later the patient was operated upon. A small uterus, both tubes and right ovary were removed. No tubercles were found in the peritoneum. Adnexal structures on both sides were matted together; both tubes were thickened and nodular. The bowel or bladder was not adherent. Evidence of tuberculosis was found in the adnexal structures. The vagina continued to heal except for the extreme apex. It was felt that the operative procedures were justified because of the opportunity of removing the only known focus of infection. The apex of the vaginal vault did become constricted and occasionally drains a small amount of mucopurulent material.—*Genital Tuberculosis with Atresia of the Vagina and Amenorrhea*, R. T. Schmidt & R. L. Faulkner, *Am. J. Obst. & Gynec.*, April, 1947, 53: 695.—(R. W. Clarke)

Tuberculosis of Uterus.—Only 191 cases of tuberculosis of the cervix have been recorded, of which 44 were thought to originate in the cervix itself. Pathogenesis of the lesion is by hematogenous dissemination from a visceral focus or by an ascending infection from a primary genital lesion. Diagnosis of the disease is made by pathological examination of the resected cervix, in which tubercles are seen in the glandular stroma and in which acid-fast bacilli may be demonstrated by proper staining. Clinically, the patient may present symptoms and signs of a chronic cervicitis; pelvic examination reveals signs consistent with carcinoma: a large, firm, ulcerated cervix, fixed in position. Tuberculosis of the cervix in a 51-year-old married woman is reported in whom a subtotal hysterectomy had been performed some eighteen years

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formerly because of uterine fibroids. Pre-operative diagnosis was procidentia, although after removal of the cervix, histological examination showed typical tubercles in areas of chronic inflammation associated with tubercle bacilli. Her chest film revealed scarring in the apices. Complete urological studies failed to reveal any evidence of tuberculous infection.—*Tuberculosis of the Cervix Uteri*, G. L. Beckner, *Ann. West. Med. & Surg.*, April, 1947, 1: 74.—(P. Q. Edwards)

Tuberculosis of Spine.—Tuberculosis of the spine in children should be treated by fusion of the posterior elements of the vertebral bodies involved to allow healing with minimal deformity. The degree of kyphosis will depend upon the amount of involvement in the cancellous bone. This orthopedic procedure is usually performed in stages—hemifusion—to reduce postoperative complications. In so far as tuberculosis of the spine represents only one aspect of a generalized disease, vertebral foci, if not treated, may continue to exist after the pulmonary disease is controlled. Spinal fusion is the treatment of choice not only to eliminate active foci but to prevent deformities due to destruction of vertebral bodies.—*Treatment of Tuberculosis of the Spine in Children*, W. E. Swift, *Quart. Bull. Sea View Hosp.*, October, 1946, 8: 360.—(P. Q. Edwards)

Tuberculosis of Brain and Meninges.—Tuberculoma was once the most common intracranial tumor. It is now relatively rare. It is an expanding lesion. There are signs both of increased intracranial pressure and of focalization. The chief conditions from which it must be differentiated are tumor and abscess. Although operation increases the risk of tuberculous meningitis, it must, nevertheless, be done. In 6 of the authors' cases subjected to operation, there were 4 recoveries; 2 patients died from meningitis. Of 25 cases, one-half were over 10 years old. The onset is insidious with the prodromal period ranging from seven days to six months. Neurological signs may be divided into five groups: (1)

Meningeal irritation; these signs may be absent in infants. (2) Increased intracranial pressure, characterized by headache, vomiting and increased spinal fluid pressure. (3) Mental changes, consisting of irritability, apathy and stupor. (4) Epilepsy; 8 of 25 cases had convulsions; this is more common in children. (5) Focal signs; these are very common, particularly those related to the innervation of the eye muscles. There was an abnormal plantar response in 16 cases. Pathological studies show extensive vascular changes in the meninges. These result in secondary changes in the brain tissue. Either the protein or the cell count in the cerebrospinal fluid, usually both, is elevated. The pleocytosis is chiefly lymphocytic though rarely 100 per cent. There is a progressive fall in chlorides particularly in the latter stages. However, there is no pathognomonic level. The condition must be differentiated from pyogenic meningitis, poliomyelitis and brain tumor. In differentiation from pyogenic meningitis, a history of tuberculosis elsewhere in the body or in the patient's family is of great importance. When in doubt, treatment should be for the pyogenic condition.—*Some Clinical and Pathological Aspects of Tuberculosis of the Central Nervous System*, H. V. Smith & P. Daniel, *Tubercle*, April, 1947, 28: 64.—(A. G. Cohen)

Treatment of Lupus Vulgaris.—One hundred and fifty cases of lupus vulgaris were treated for at least four months with calciferol in daily doses of 100,000 units. Prior to calciferol, the best forms of treatment had resulted in failures in 20 per cent of cases. The new treatment has not changed these figures, but it is a great advance in that it is much simpler and has shortened the time of treatment by one-half to two-thirds. Previous X-ray or radium treatment made no difference in the results. Intolerance to the drug was encountered in 23 per cent of cases. The addition of calcium was found to be unnecessary. The addition of vitamin B was without effect in preventing reactions. Later in the study, calciferol, in daily doses of 500,-

000 to 3,000,000 units, was given to patients with pulmonary tuberculosis. No beneficial effects were noted.—*Calciferol in Tuberculosis*, P. J. Feeny, E. L. Sandiland & L. M. Franklin, *Lancet*, April 5, 1947, 1: 459.—(A. G. Cohen)

original work.—*La streptomycine*, L. de Gennes & Minne, *Presse méd.*, March 22, 1947, 55: 202.—(E. Bogen)

Antibiotic against Mycobacteria.—An actinomycete (A-82) formed an antibiotic which when tested against more than 60 species, including more than 20 genera of bacteria, inhibited only *M. smegmatis*, *M. phlei* and a nonpathogenic, rapidly growing strain of *M. tuberculosis*, variety *hominis* No. 607. A pathogenic *M. tuberculosis*, variety *bovis*, was not inhibited. Methods for producing the crude antismegmatis factor were outlined. It was thermostable and more active in alkaline media than in acid media.—*An Antibiotic (Anti-Smegmatis Factor) Produced by an Actinomycete, Specifically Inhibiting Species of Mycobacterium*, A. Kellner & H. E. Morton, *Proc. Soc. Exper. Biol. & Med.*, November, 1946, 63: 227.—(F. B. Scibert)

Fusarium Inhibiting Tubercle Bacilli.—Of a large number of fungi, recently isolated from a variety of sources, only one, a *Fusarium*, *Sp.*, inhibited growth of the tubercle bacilli. An alundun capsule was introduced into an Erlenmeyer flask containing Long's media and the fluid inside the capsule was inoculated with the fungus while the outside fluid was inoculated with a recently isolated strain of virulent tubercle bacilli. The inhibiting substance passed through fritted glass filters and Mandler filters but was partially inactivated by passage through Seitz filters. The crude filtrate was active up to a dilution of one-twentieth and withstood heating to 100°C. for fifteen minutes without loss of activity.—*Growth Inhibition of Tubercle Bacilli by Fusarium Sp.*, C. H. Boissevain, *Proc. Soc. Exper. Biol. & Med.*, December, 1946, 63: 555.—(F. B. Scibert)

Streptomycin.—A review of the American studies on streptomycin, citing 43 references (with several typographical errors), but no

Streptomycin in Experimental Tuberculosis.—The *in vitro* retarding influence of streptomycin on tubercle bacilli is accentuated in poor nutrient media, and diminishes one hundred-fold in good media. In egg-yolk-glycerol medium 1,000 units of streptomycin were required to retard the growth of a 0.01 mg. inoculum of virulent tubercle bacilli (human type). Twenty thousand units injected intravenously into guinea pigs fifteen minutes before bleeding were required to inhibit completely the growth of human type tubercle bacilli planted in media to which the blood was added; 10,000 units of streptomycin left in contact with 10 mg. of virulent tubercle bacilli in a saline suspension for one week did not destroy the organisms, and had no effect after one week's contact with 0.01 mg. per cc. of tubercle bacilli suspended in blood. In 4 guinea pigs inoculated intravenously with 1 mg. of tubercle bacilli and treated immediately with 9,000 units daily subcutaneously for twenty-eight days, the average survival period was thirty days, compared to eighteen days for 4 control animals. One pig survived forty-three days, dying fifteen days after treatment was stopped; it showed a heavy growth of tubercle bacilli in its organs. Streptomycin definitely retards the course of tuberculosis in guinea pigs, but the effect lasts only as long as the treatment continues, and there is no destruction of all the tubercle bacilli by the amounts of the drug used. No accumulation of the drug in the tissues was found, nor adsorption of the drug by the tubercle bacilli or tubercles. Up to one-half million units of streptomycin per kilogram daily subcutaneously did not eradicate the infection in mice. It is concluded that the drug is not tuberculocidal in reasonable amounts, but that it interferes with the anabolism of the bacilli, retarding growth. Even this requires high concentrations of the drug, and such high levels can be obtained *in vivo* only briefly with the present potency of

material. In clinical tuberculosis the reproduction and growth of tubercle bacilli is irregular and occurs over long periods of time. The applicability of streptomycin to human tuberculosis is limited.—*The Tubercle Bacillus and Fundamental Chemotherapeutic and Antibiotic Action*, H. J. Corper & M. L. Cohn, *Yale J. Biol. & Med.*, October, 1946, 19: 1.—(A. A. Cohen)

Streptomycin Resistance of Tubercle Bacilli.—Tubercle bacilli isolated from guinea pigs inoculated with sputum, urine or material obtained on gastric lavage from tuberculous patients, who were being treated with streptomycin, were as resistant as cultures isolated directly from the same materials. Cultures of tubercle bacilli from patients receiving streptomycin retain their resistance to the drug even after residence in guinea pigs for ten weeks or more and subsequent maintenance on glycerinated egg-yolk-agar for many weeks.—*Persistence of Resistance of Tubercle Bacilli to Streptomycin during Passage through Guinea Pigs*, A. G. Karlson, W. H. Feldman & H. C. Hinshaw, *Proc. Soc. Exper. Biol. & Med.*, January, 1947, 64: 6.—(F. B. Seibert)

Quantitative Effect of Streptomycin.—A simple, safe and accurate method is described for the quantitative estimation of the growth of *Mycobacterium tuberculosis* based upon turbidimetric measurements in Dubos medium. This procedure can be applied to measuring the rate and amount of growth of *M. tuberculosis* in various media, as affected by the presence of streptomycin. The turbidity was correlated with the weight of cell material and with the number of viable cells as determined by plate counts of viable bacteria in a suspension. A standard curve was prepared.—*Quantitative Measurement of Growth of Mycobacterium tuberculosis: Effect of Streptomycin*, Dorothy G. Smith, *Proc. Soc. Exper. Biol. & Med.*, January, 1947, 64: 56.—(F. B. Seibert)

Streptomycin and Diasone in Experimental Tuberculosis.—Both streptomycin and

diasone have shown some degree of therapeutic effectiveness in the treatment of experimental tuberculosis in guinea pigs. When given together they exert even greater effect, suggesting a synergistic or additive effect. Both are more effective in suppressing tuberculous infection by the institution of treatment within a few days after inoculation with virulent tubercle bacilli than in the treatment of established lesions developing two weeks or longer after infection has been established.—*Streptomycin and Diasone in the Treatment of Experimental Tuberculosis of Guinea Pigs*, F. T. Callomon, J. A. Kolmer, Anna M. Rule & A. J. Paul, *Proc. Soc. Exper. Biol. & Med.*, November, 1946, 63: 237.—(F. B. Seibert)

BCG Sensitivity to Streptomycin.—In order to test the effect of streptomycin on BCG, two series of tests were made. The drug was added in varying dilutions to Sauton fluid to which a vigorous culture of BCG was added. Daily inspection of the cultures revealed that normal growth took place in bottles containing streptomycin one unit per cc., marked inhibition in 2 units per cc. and barely visible growth in 5 units per cc. After seventeen days' incubation, the cultures were dried and weighed, showing results corresponding to the visible results. Secondary cultures were then made, which showed growth in all cases, although the number of colonies decreased as the streptomycin concentration increased. In the second experiment BCG suspensions in diluted Sauton fluid (BCG vaccine) were mixed with equal portions of streptomycin solutions making concentrations from 5 to 100 units per cc. After time intervals from one-half to twenty hours at room temperature, the mixtures were centrifuged and cultures were made from the sediment. Only after twenty hours' exposure in concentrations of 50 and 100 units per cc. were bactericidal effects observed. The bactericidal effect was markedly less pronounced on resting cells than cells undergoing growth.—*The Sensitivity of BCG to Streptomycin*, J. Bpe & Th. M. Vogelsang, *Acta*

tuberc. Scandinav., 1946, 20: 158.—(P. Q. Edwards)

Clinical Results with Streptomycin.—This is the initial report, from a U. S. Naval Hospital, on 37 patients with moderately and far advanced pulmonary tuberculosis who were treated for 120 days with streptomycin. These patients were chosen from over 1,800 tuberculous patients as fulfilling the strict criteria of having exudative type lesions which had progressed during three months of strict bed-rest and in whom other therapeutic measures were contraindicated. By the end of the course of treatment, 7 were considered ready for major surgery, 3 were nearly ready and 6 had improved to such an extent that no collapse measures were deemed necessary. Clinically the best progress was made during the first month of treatment and the reactions were generally mild and of the usual nature. During the first month following cessation of streptomycin the relapse rate was 16 per cent.—*Report on Navy Cases in Joint Army, Navy and Veterans Administration Study of Streptomycin in the Treatment of Pulmonary Tuberculosis, Armed News Letter, U. S. Navy, April 11, 1947, Vol. 9, No. 8.*—(E. A. Rouff)

Promizole and Streptomycin in Tuberculosis of Skin.—Twelve cases are reported who had various forms of cutaneous tuberculosis consisting of lupus vulgaris (3), scrofuloderma (6), tuberculosis cutis colliquativa (1), erythema induratum (1) and tuberculosis miliaris disseminata faciei (1). Seven of the 12 patients received promizole and 5 received streptomycin; 3 of the patients who had received promizole were treated subsequently with streptomycin. The average dose of promizole was from 8 to 10 g. daily, administered orally. Streptomycin was usually given in doses of approximately 1 g. per day as streptomycin salt in an aqueous solution. Approximately 125 mg. was injected intramuscularly every three hours. The total dosage per course of treatment varied from 15 to 128 g. Of those receiving only promizole,

one case of scrofuloderma was unimproved and one considerably improved; a case of lupus vulgaris was unimproved, and a case of erythema induratum (legs) was temporarily healed, but partially relapsed a year later. Of those receiving only streptomycin 3 cases of scrofuloderma were improved, one doing very well. Relapses occurred, however, except in the latter case. A case of tuberculosis miliaris disseminata faciei developed temporary remissions after each of three courses of streptomycin treatment. And, lastly, the case of tuberculosis cutis colliquativa did well despite inadequate treatment. Of the 3 cases receiving promizole first and streptomycin later, one case of lupus vulgaris, failing to improve on promizole, did very well on streptomycin, another case of lupus gave indifferent results and a case of scrofuloderma did fairly well but with a tendency to relapse. It is probable that the results of treatment of early primary infections, such as inoculation tuberculosis of the skin will be better than in the treatment of long-standing organized processes or extensive "id" reactions in which few tubercle bacilli are present. The possibility that, in the patients with sinuses and ulceration, the drugs used might have been effective primarily against the secondary bacterial invaders has not been overlooked, but this appears improbable because of the limited range of action of these substances and the failure of other antibacterial agents in similar circumstances. Streptomycin, although not the ideal agent for the treatment of cutaneous tuberculosis, is of enough value to warrant further investigation and use. (Illustrated in color)—*Treatment of Various Types of Cutaneous Tuberculosis with Promizole and Streptomycin*, P. A. O'Leary, E. T. Ceder, H. C. Hinshaw & W. H. Feldman, *Arch. Dermat. & Syph.*, February, 1947, 55: 222.—(J. S. Woolley)

Chemotherapy of Iodonium and Sulfonium Compounds.—Only the iodonium compounds inhibited the growth of tubercle bacilli *in vivo* but they had no significant therapeutic action.—*Chemotherapy of Certain Iodonium and Sulfonium Compounds*, B. L. Freedlander &

F. French, *Proc. Soc. Exper. Biol. & Med.*, November, 1946, 63: 319.—(F. B. Seibert)

Chemotherapy with Diphenylsulfone Derivatives.—A series of derivatives of diphenylsulfone, sulfoxide and sulfide were tested for *in vitro* tuberculostatic activity and for antituberculous therapeutic activity in guinea pigs. The following compounds in addition to the reference materials, 4,4'-diaminodiphenyl-sulfone and its derivative diasone, showed high *in vivo* activity: 4-benzylideneamino, 4'-aminodiphenylsulfone; 4-nitro, 4'-acetyl-aminosulfoxide (hypo): 4,4'-diacetyl-aminodiphenylsulfoxide (oral). 4-Chloro, 4'-aminodiphenylsulfide and the corresponding iodo derivative were highly tuberculostatic *in vitro* but were devoid of *in vivo* activity.—*Derivatives of Diphenylsulfone, Related Sulfoxides and Sulfides in Experimental Tuberculosis*, B. L. Freedlander & F. French, *Proc. Soc. Exper. Biol. & Med.*, November, 1946, 63: 361.—(F. B. Seibert)

Complications with Diasone.—Severe toxic reactions were encountered in 2 patients during the use of usual therapeutic doses of diasone. In each case cyanosis was the first sign, followed rapidly by dyspnea, fever, exanthematous rash leading to bullae and exfoliation and marked reduction in red cells. One of the patients had a hemolytic reaction, with severe anemia and jaundice. Because of these serious, near fatal, reactions in 2 out of 14 patients treated with diasone for less than one month, the opinion is expressed that this drug should be discarded permanently and be replaced by a less toxic substance.—*Complications in Connection with the Use of Diasone in Tuberculosis*, E. Hedvall, *Acta tuberc. Scandinv.*, 1946, 20: 164.—(P. Q. Edwards)

Pulmonary Changes after BCG Vaccination.—Pathological pulmonary shadows in BCG-vaccinated children are difficult to interpret, particularly when veil-like infiltrations and associated hilar indurations persist on the roentgenogram for only one to two months. A study of 9 such cases is reported,

in which the diagnosis of primary tuberculosis was made in 2 cases in spite of failure to find bacilli. In each of these patients, there had been some question regarding the immunological response to BCG; one of these children may have been infected with tuberculosis before the vaccination. Two of the 9 cases were found to have atypical virus pneumonia by demonstration of cold autohemagglutinins in their sera. The 5 other cases had pulmonary changes of a much shorter duration than is characteristic of primary tuberculosis. Wallgren states that primary tuberculosis causes shadows to persist for six months before showing regression. These children had infiltrations lasting but one to two months, associated with increased sedimentation rates and brief periods of fever in several cases. The possibility of a more benign, shortened course for primary tuberculosis in BCG-vaccinated children should be considered, although the diagnosis of atypical virus pneumonia seems more likely in view of the absence of bacilli by gastric examinations in all cases, the brief or absent febrile period and the typically evanescent veil-like infiltrations in the parenchyma of the lungs. Unfortunately, cold autohemagglutinins were not tested for in 5 of these patients, which might have confirmed the diagnosis of virus pneumonia.—*Roentgenological Pulmonary Changes in BCG Vaccinated Children*, G. Birke, *Acta tuberc. Scandinv.*, 1946, 20: 107.—(P. Q. Edwards)

Lupus following BCG.—Although BCG vaccination may occasionally give rise to abscess formation at the site of injection or a regional lymphadenitis, this is the first known case of post-vaccination lupus vulgaris developing over the area used for injection. The patient was a 16-year-old workman who was vaccinated with BCG in his left deltoid region. Ulceration appeared soon afterwards, followed by a slowly spreading lesion which became 7 x 6 cm. in size within six months. Local treatment with pyrogallie acid ointment seemed to produce temporary healing, soon to be followed by necrosis and

ulceration with typical nodules along the margins. Ten series of treatments with the Finsen light resulted in excellent improvement. Curiously, the patient still had a relatively weak reaction to 0.01 mg. of tuberculin, although his sedimentation rate was considerably increased.—*Lupus Vulgaris Developed in the Reaction to a Calmette Vaccination*, S. Lumholt, *Acta tuberc. Scandnav.*, 1946, 20: 136.—(P. Q. Edwards)

Stain for Tubercle Bacilli.—Osol's method, in which acid-fast bacilli are stained with steaming carbol fuchsin and decolorized both with acid alcohol and sodium hyposulfite without counterstaining, was tried on 141 sputa and 100 gastric specimens. It was useful, especially with specimens containing rare bacilli, but has relatively numerous sources of error and cannot replace the usual Ziehl-Neelsen technique.—*La methode d'Osol dans la recherche des bacilles de Koch*, B. Wissmer, *Presse méd.*, March 15, 1947, 55: 181.—(E. Bogen)

Carbol-Night-Blue Stain for Tubercle Bacilli.—Sputa and tissue sections stained with an alcoholic solution of night-blue in carbolic acid and counterstained with chrysoidin revealed more tubercle bacilli than Ziehl-Neelsen stains. Specimens negative by one method were also free of bacilli by the other.—*J. Quandt, Zentralbl. f. Bakt. u. Infektionskr.*, 1944, 151: 340.—(B. Gersl)

Respiration of Tubercle Bacillus.—Respiration of tubercle bacilli varies not only for a single species according to the particular strain, but also for a single strain according to the growth conditions which have been imposed upon it. Even when consumption of the medium is equally intense for two strains of the same species, their respirations can nevertheless be different, depending upon the use to which the bacilli put the consumed medium. Energy expenditures exacted by the culture being different for a single species according to the strain, bacilli of a certain strain may fix, at the time of multiplication,

more carbon than the bacilli of another strain, and, consequently, form less carbon dioxide (consume less oxygen) at the expense of an equal quantity of carbonated compound. It is thus that, in certain cases, virulent variants, in order to form an equal weight of culture during a time, destroy more of the medium than attenuated variants. However, one may not conclude from these preliminary studies that a direct correlation exists between virulence and respiratory exchanges of tubercle bacilli.—*Les échanges respiratoires de bacilles tuberculeux de souches différentes*, A. Andrejew, *Ann. Inst. Pasteur, March*, 1947, 73: 235.—(P. Q. Edwards)

Virulence of Tubercle Bacilli.—Since intravenous injections of very small numbers of tubercle bacilli into guinea pigs for virulence tests offer distinct advantages over subcutaneous injections, a method is described for locating suitable viens in the animals' legs. To obtain suspensions free of clumps of bacteria, filtering and centrifugation are employed for an optimal period of time. To determine the content of tubercle bacilli in such suspensions, a modification of Wright's method is described, wherein a suspension of ordinary baker's yeast is used in place of red cells, as the latter usually disintegrate during staining. This control suspension of yeast is mixed with the suspension of tubercle bacilli in suitable proportions, a smear is made from the mixture which is stained by the Ziehl-Neelsen technique. In a good preparation, bacilli and yeast cells lie singly and evenly distributed 2 to 4 per field. At least 200 cells or bacteria are counted. With such a technique, virulence tests have been carried out on various strains isolated from sputum in an effort to find a highly virulent human strain for experimental work.—*Virulence Tests on Tubercle Bacilli*, G. Widström, *Acta tuberc. Scandnav.*, 1946, 20: 171.—(P. Q. Edwards)

Superinfection of Tuberculous Rabbits.—In genetically similar rabbits, there was no difference in the rate of progression of disease whether the contact remained in continuous

exposure to the contagion or whether it was removed therefrom immediately after the acquisition of a positive tuberculin reaction. The contagion to which the rabbits were exposed was very high so that the incidence of acquired disease was 73 per cent in the resistant (A) family and 85 per cent in the less resistant (C) family. The duration of the disease of the A rabbits, both those exposed and those not exposed to superinfection, was longer, an average of 4.6 and 5.4 months, as compared with 3.6 and 3.9 months, respectively, for the rabbits of low resistance. As in previous studies the A rabbits tended to acquire tuberculin sensitivity more rapidly than the C rabbits, their allergy was less developed during the course of their disease and the progression of the infection was slower and anatomically more chronic.—*Effect of Exogenous Superinfection on Naturally Acquired Bovine Tuberculosis in Inbred Rabbits*, M. B. Laurie & Joyce Becker, *Proc. Soc. Exper. Biol. & Med.*, November, 1946, 63: 465.—(F. B. Seibert)

Pyogenic Infection in Tuberculosis.—Pyogenic infections, especially those occurring in the pharynx and mouth and spreading along the lymphatics toward the hilum, are of great importance in the pathogenesis of tuberculosis, according to Westergren. In trying to approach more closely the natural mode of infection by the upper respiratory tract, guinea pigs were inoculated intravenously with a measured amount of tubercle bacilli to which additional intranasal and submucous injections with *Streptococcus viridans* were given. Results showed that guinea pigs infected with tuberculosis, both those killed and those dying spontaneously, were all not only infected with tuberculosis but also with two, often three, different species of pyogenic bacteria. Although the *Streptococcus viridans* used proved to be nonpathogenic for the animals, the induced tuberculous infection gave rise to activation of latent organisms already present in the animal, as opposed to the control nontuberculous animals in which the same pyogens were found by culturing the

respiratory passages. Intranasal instillation of broth also appeared to activate latent infections in nontuberculous animals, although spontaneous recovery usually took place. If, however, the installations were performed on tuberculous infected guinea pigs, the activated pyogenic infections took a malignant course which in turn accelerated the progress of the tuberculosis. Applicability of these finding to human tuberculosis seems possibly of importance.—*Multiple Infection in Experimental Tuberculosis in Animals*, T. Packalén, *Acta tuberc. Scandinv.*, 1946, 20: 199.—(P. Q. Edwards)

Weltmann Reaction in Tuberculosis.—The Weltmann reaction, both in its original form and its nephelometric modification by Wuhrmann and Wunderly, together with sedimentation rate and Takata reaction were studied in 100 cases of exudative pulmonary tuberculosis. A low nephelometric curve (below 400 units) or a moderately high one combined with a shift of the Weltmann curve to the left indicates a poor prognosis. A high nephelometric curve (above 550 units) in the presence of left shift suggests improvement. The Takata reaction proved of no value.—*Zur Humoralpathologie der Lungentuberkulose*, A. Pedrazzini, *Schweiz. Ztschr. f. Tuberk.*, 1946, 3: 373.—(B. Gerstl)

Diagnostic Bronchial Lavage.—In 10 apparently arrested patients, in all of whom the sputum had been negative for some time, bronchial washings proved positive in 6. While the method was apparently harmless in these cases, it seems inadvisable to try it in patients with bronchial asthma, low vital capacity or decompensated heart disease. Abreu's series at the Sao Sebastiao Hospital at Rio includes 313 cases. Positive results in Abreu's cases were 15.3 per cent.—*Diagnostic Bronchial Lavage*, M. M. Bueno, *Clin. tisiol.*, July-September, 1946, 1: 222.—(A. A. Moll)

BCG Vaccination in Sarcoidosis.—Interest in a diagnostic test for Schaumann's disease

- (*lymphogranulomatosis benigna*) has led to some experimental work with various types of techniques for BCG vaccination in an effort to determine the most efficacious method for production of a satisfactory and easily obtained biopsy specimen for pathological diagnosis. Rosenthal's percutaneous BCG vaccination method has been modified by Birkhaug by the use of a metal spring lancet which produces uniform punctures through a thin tissue paper soaked in vaccine. In a series of 92 people so vaccinated, 72 became positive to tuberculin; of these, only half became positive within three to four weeks following vaccination—a very small percentage when compared with results reported by Rosenthal and other investigators using the intracutaneous technique. In an effort to reproduce Lemming's attempts to obtain biopsy material for diagnosis of sarcoidosis, two series of patients were vaccinated by the above technique: several normal tuberculin-negative patients and 5 tuberculous (tuberculin-positive) patients. Excision of several of the small papules resulting from the vaccination was performed for pathological examination. No essential differences were found between the two groups of patients—both showed characteristic masses of polynuclear cells and histiocytes in the subcutaneous tissues. Patients with sarcoidosis are frequently tuberculin-negative, which suggests that the disease may be a type of tuberculosis with particular allergic conditions, a so-called positive anergy, including a high degree of immunity towards tuberculin. This condition further implies such a rapid destruction of tuberculin that the skin test invariably is negative. Lemming found that patients with sarcoidosis remained negative even when large doses of BCG were administered intracutaneously. Biopsy of a regional node after vaccination showed changes typical of sarcoidosis. In another case, cutaneous changes at the site of vaccination were both macro- and microscopically similar to skin manifestations of the disease. This type of evidence makes it seem theoretically possible that the Rosenthal-Birkhaug vaccination with subsequent excision of one or more papules after a suitable time interval might provide a relatively simple method for direct patho-anatomical diagnosis. Several patients with sarcoidosis have been vaccinated but in no case has the excised papule shown diagnostic changes. One case at another hospital has been reported, however, in which the diagnosis was made by examination of the post-vaccination nodule.—*On the Value of the Percutaneous BCG-Vaccination According to Rosenthal, O. Forssman, Acta tuberc. Scandinav., 1946, 20: 123.*—(P. Q. Edwards)
- Sarcoidosis and Fungus Infection.**—A general survey of the literature relating to the etiology of sarcoidosis is followed in this paper by detailed case histories of 8 patients in whom the clinical and roentgenological findings were indistinguishable from sarcoidosis; yet in each instance exposure to dust, moulds, or "burnt" grain in connection with threshing preceded development of symptoms. *Monilia* organisms were regularly demonstrated in the sputum of each patient. Many features of sarcoidosis point to a dust infection, with the upper respiratory passages, tonsils, lungs and conjunctivae as portals of entry. Subsequent spread by lymphatic channels ordinarily takes place, producing a disease closely resembling primary bronchomycoses with bilateral hilar adenopathy. Both in sarcoidosis and in similar syndromes arising in connection with the inhalation of fungi, there is often a prolonged tuberculin anergy or disappearance of a previously positive tuberculin skin reaction. Because of the history in each of these 8 cases of inhalation of dust while harvesting grain, feeding cattle or cleaning mouldy cellars and subsequent demonstration of *monilia* in the sputum, the original diagnosis of sarcoidosis was changed to bronchomycosis, in spite of the typical clinical, X-ray and patho-anatomical picture ordinarily designated as sarcoidosis. Localization and course of sarcoidosis agree more closely with a fungoid infection than with tuberculosis.—*Is Sarcoidosis a Fungoid Disease?, E. Törnell, Acta tuberc. Scandinav., 1946, 20: 212.*—(P. Q. Edwards)

Pulmonary Hydatid Cysts.—Conservative measures which have been used in the treatment of simple univesicular cysts are reviewed critically: (1) Expectant; with the hope that spontaneous expectoration will occur; there is great probability that the disease will progress. (2) Aspiration; while this has produced many cures there are also many dangers. (3) Artificial pneumothorax; this is very dangerous; it may cause rupture of the cyst with expectoration into a bronchus or expulsion into the pleural cavity. (4) Drugs and radiotherapy; these are of no value. (5) Bronchoscopy; this is of no value. In 133 reported cases in which hydatid cysts were coughed up, there were 31 deaths. In children, the greater frequency of spontaneous rupture, as well as the greater surgical risk, have been advanced as arguments for conservative therapy. The author disagrees with this reasoning. Upper lobe cysts are supposed to have a greater chance to be expectorated spontaneously. The dangers of operation upon cysts near the hilum are said to be greater. In both of these instances, the author disagrees with suggestions that conservative treatment is preferable. The only cases in which waiting is approved are those in which the cysts are very small. On the day prior to operation, a small pneumothorax is induced. If there are no adhesions, a thoracotomy is done. The cyst is located and packed off; it is then aspirated slowly but not tapped dry. Incision is made through the adventitia down to the laminated membrane. The cyst is removed easily. The incision in the adventitia is closed. The suture line is covered with visceral pleura. A catheter is left in the pleural space. Lobectomy is advised: (1) when the cyst is almost as large as the lobe, (2) when the cyst is old and has a tough adventitia and (3) for simple cysts which have caused bronchiectasis or pulmonary suppuration. In cases of simple bilateral hydatids, the treatment is the same. The treatment of complicated cysts is varied: (1) Daughter cysts; these result from a) previous spontaneous "cure" or b) hydatid fluid having been spilled at a previous operative site. The treatment is like that of a

simple cyst. (2) Ruptured and infected cysts; lobectomy is indicated. (3) When a liver hydatid has ruptured into the thorax, a) the lesion is drained as widely as possible, b) all the hydatid elements are removed and c) later the degree of pulmonary damage is assessed and the diseased portion of lung is removed. (4) A persistent empty sac; this may be a source of hemorrhage or infection and lobectomy is indicated. Thoracoplasty and phrenic paralysis are of no value. (5) A dead cyst. This is dangerous and a lobectomy must be done.—*The Treatment of Pulmonary Hydatid Disease*, N. R. Barrett, *Thorax*, March, 1947, 2: 21.—(A. G. Cohen)

Syphilis of Lung.—Acquired chronic pulmonary syphilis is uncommon and often not recognized, though clinical recognition is becoming more frequent. It occurs five to ten years after infection, and more often in males than in females, but fatal progression is more common in females. A syphilitic pneumonitis may occur during early infection by an extension from syphilids in the upper respiratory tract, but the more common lung lesions are those in late syphilis, often in association with aortitis. The onset of the chronic form is insidious; symptoms are often lacking, and when present, are those of any chronic pulmonary lesion; physical signs depend upon the location, extent and character of the lesion. Frequent X-ray examinations are the great hope for a more frequent diagnosis. The usual chronic forms are gummata and interstitial sclerosis, with bronchiectasis being a possibility. The most notable histopathological difference from tuberculosis is the occurrence of necrosis *after* fibrosis in the syphilitic lesions. It is hardly possible to describe specific roentgen signs. The lesions may be discrete rounded densities, densities surrounded by exudate or linear fibrosis. They occur most often in the lower half of the lungs, and especially in the right lung. They often are in hilar and truncal locations, but may be subpleural. Clearance of the lesions during antisymphilitic therapy, using an X-ray method as a control, is the best presumptive proof of

ABSTRACTS

the diagnosis. Resolution of the lesion, leaving fibrous scars, is the typical result. Four cases are reported; three were treated, one with penicillin, and clearing and residual fibrosis occurred.—*The Clinical, Radiologic, and Pathologic Aspects of Late Pulmonary Syphilis*—F. Windholz, *Am. J. Syph., Gonorr. & Ven. Dis.*, March, 1947, 31: 166.—(W. H. Oatway, Jr.)

Actinomycosis.—Among 240 patients with chronic bronchopulmonary infections, observed from May to November, 1945, *actinomyces bovis* (Israel) was isolated, by direct examination and culture from the sputum in 109 and from bronchoscopic specimens in 65. *Actinomyces bovis* may be an inhabitant of the normal mouth and the above observations indicate that it may also be frequently found in various types of bronchopulmonary infections. This occurs as a result of aspiration of oral and pharyngeal material in individuals whose defenses against aspiration have been weakened by infection. The presence of actinomyces in the lung is of no clinical significance in most instances until anaerobic conditions occur, such as blocking of a bronchus by a plug of exudate. Approximately 50 per cent of the patients with bronchiectasis had actinomyces in material obtained by bronchoscopy. There was nothing characteristic about this group except that the sputum appeared to be more copious, more foul and more frequently bloody than when the fungus was not present. Many of these patients were benefited by intratracheal penicillin and in several the fungus disappeared. Twenty patients from whom actinomyces was isolated by bronchoscopic aspiration are discussed in greater detail. These fell clinically into the following groups: chronic pneumonitis, lung abscess and pulmonary suppuration. Various other organisms were almost always present in the exudate. The onset of the pulmonary infection was usually insidious with low-grade symptoms. Sputum was foul and bloody in all patients. Oral hygiene was invariably poor and actinomyces was frequently isolated from tonsillar crypts, dirty gums and periapical abscesses. Bronchoscopic appearance was not specific. Penicillin or penicillin plus sulfadiazine, both in large doses, were the most effective medical treatment. *In vitro* experiments suggest the even greater efficacy of streptomycin in inhibiting the growth of actinomyces but further clinical experience is needed. Five patients without cavitation responded excellently to medical treatment which was continued for a period of eight to twelve weeks. An abscess healed on medical treatment in only one patient. Cavitory cases usually required surgery in the form of drainage or resection. The involved pulmonary tissue was markedly fibrotic. Actinomyces were readily isolated from abscesses in resected lungs. The presence of the fungus is less of a factor in influencing the clinical course than the mechanical factors of bronchial occlusion, tissue destruction and fibrosis. It is debatable whether these cases should be classified as pulmonary actinomycosis or rather as pulmonary suppurative disease in which the fungus is present. The clinical course did not appear significantly different from those cases in which the fungus was not present. All patients were treated similarly without reference to the fungus. Actinomyces was not responsible for any postoperative complications in this group. Three patients with abscesses were cured by external drainage; apparent cures have resulted following pneumonectomy in 2 and following lobectomy in 4.—*Bronchopulmonary Actinomycosis*, E. B. Kay, *Ann. Int. Med.*, April, 1947, 26: 581.—(H. R. Nayer)

Histoplasmosis.—Histoplasmosis was demonstrated in a 7-months-old girl with anemia, leukopenia and hepatosplenomegaly, by bone marrow biopsy, histoplasmin skin test and positive cultures from blood, marrow, stool and duodenal contents. Necropsy showed wide-spread dissemination of intracellular yeast forms throughout the body. Culture on 7 per cent horse blood agar containing 20 units per cc. each of penicillin and

streptomycin at 32° and 38° C. yielded abundant filamentous forms in which characteristic tuberculate chlamydospores developed, from all tissues and fluids tested, except the bile and cerebrospinal fluid.—*Histoplasmosis in Infancy: The Pathologic Picture as Seen in One Case*, L. A. Weed, A. M. Iams & H. M. Keith, *Arch. Path., February, 1947, 43: 155.*—(E. Bogen)

Histoplasmin Sensitivity.—Charleston, South Carolina is in an area of known low histoplasmin sensitivity (about 2 per cent). A study was made of 494 school children by chest X-ray films and tuberculin tests. Seventy-two per cent (356 individuals) were nonreactors. Seven of these had calcifications in the lung by X-ray film. Four of the 7 reacted to histoplasmin. All of the 4 had previously lived in an area with a high incidence of sensitivity (Kentucky, Mississippi, Tennessee or Alabama).—*Pulmonary Calcifications and Sensitivity to Histoplasmin in Charleston, S. C.*, J. I. Waring & D. B. Gregg, *Am. J. Dis. Child., February, 1947, 73: 189.*—(W. H. Oatway, Jr.)

Pulmonary Calcifications.—A series of 110,000 consecutive 35 mm. chest photo-fluorographic examinations performed at a naval training centre were reviewed and 102 cases, an incidence of less than 0.1 per cent, were rechecked by conventional 14" x 17" films. Of these, 21 were found to show uniformly distributed calcified lesions, usually all of the same size and called "disseminated miliary calcifications." The remainder, 81, demonstrated multiple calcified lesions irregularly scattered in the hila and lung parenchyma without symmetrical distribution and of varying size. All of these cases were of a disqualifying nature for entrance into the naval service. It is recommended that such cases be further investigated to determine the exact nature of the lesions.—*Multiple Pulmonary Calcifications*, A. C. Wyman, *U. S. Nav. M. Bull., March-April, 1947, 27: 244.*—(E. A. Rouff)

Rheumatic Pneumonia.—The term "rheumatic pneumonia" has been applied by some observers to characteristic pulmonary changes described in the course of active rheumatic fever. The precise relationship of these changes to rheumatic fever is not entirely clear. The possibility also exists that these pulmonary findings may be attributed, in part at least, to cardiac failure. Grossly, the lungs are rubbery and present a surface mottled with focal hemorrhages. Thickening of the alveolar walls, capillary engorgement and edema of the interstitial tissues are seen in the acute stages. In the chronic stage, there is considerable fibrosis of the alveolar walls with narrowing of the vascular bed. The alveolar exudate, hemorrhagic and fibrinous at the onset, gradually undergoes fibrous organization. Mononuclear cells are characteristically present in this exudate; large basophilic cells of the Aschoff type have also been observed. An hyaline pseudo-membrane is frequently present, covering the walls of the respiratory bronchioles. Fibrinous and destructive changes have been described in the walls of pulmonary and systemic arterioles. The presence of Aschoff bodies in the lungs has been noted but not confirmed. Clinical descriptions have differentiated a fleeting, clinically insignificant pneumonitis and a rapidly developing wide-spread and often fatal pneumonia. The authors have attempted to clarify the clinical and roentgen picture of this type of pneumonia by a survey of 6 autopsied cases of unequivocal rheumatic fever with carditis and characteristic anatomical pulmonary findings as described above. In all 6, there was an abrupt onset of acute respiratory distress. Dyspnea, cyanosis and orthopnea were constant features. Cough was dry and hacking, sputum scant and occasionally bloody, never rusty or purulent. Pathogenic organisms were usually absent from the sputum. Fever ranged from 100° to 105° F. Physical signs were scant. One patient developed a large bilateral effusion. The white count ranged from 14,000 to 26,000, with a polymorphonuclear leucocytosis. The roentgen appearance of the pneumonia was in

distinguishable from that usually associated with cardiac failure. The presence of usually multilobar and non-segmental infiltrations is of some value in ruling out bacterial and atypical pneumonia. Salicylates and penicillin did not alter the course of the disease. The carditis was in an active phase in all these patients; the diagnosis of rheumatic pneumonia should not be made in the absence of active carditis. Another significant differential consideration is the infrequency of bacterial pneumonia in active rheumatic fever; it occurred only twice in 100 attacks observed by the authors and both were pneumonitis on a bronchiectatic basis. No instances of lobar or atypical pneumonia were observed in this group. The presence of rheumatic pneumonia appears to carry grave prognostic significance.—*Rheumatic Pneumonia*, D. W. Seldin, H. S. Kaplan & H. Bunting, *Ann. Int. Med.*, April, 1947, 26: 496.—(H. R. Nayer)

Rheumatic Pneumonia.—The lesions of rheumatic pneumonia may be specific, and allergic in their genesis and manifestations. A typical sequence of several phases has been described. Two new cases of rheumatic pneumonia are reported. Together they show most of the features of an exudative lesion resulting from injury to capillary endothelium, and parallel the findings in experimental anaphylactic pneumonitis. The histories also agree with the allergic concept, and stress a possible interval following subsidence of the symptoms of endocarditis.—*Rheumatic Pneumonia*, J. I. Mossberger, *J. Pediat.*, February, 1947, 30: 119.—(W. H. Oatway, Jr.)

Congenital Bronchiectasis.—In a 13-year-old girl with a history of symptoms since the age of 4, the congenital nature of the bilateral bronchiectasis was evidenced by its association with situs transversus and nasal polyposis, the characteristic triad of Kartagener. In a 19-year-old man with bilateral bronchiectasis there were marked deformations of the thorax with anomalies of the ribs indicating a congenital origin. In both cases repeated unilateral pleural effusions were encountered.

Such recurring unilateral pleural effusions in the course of bronchiectasis are asserted to be presumptive, if not pathognomonic of a congenital origin of the bronchiectasis.—*Les bronchiectasies congénitales*, P. Lagesse & P. Buffard, *Presse méd.*, March 19, 1947, 55: 197.—(E. Bogen)

Segmental Bronchitis.—Bronchitis is not always, as commonly believed, a diffuse and generalized inflammation of the entire bronchial tree. Endoscopic examinations in both acute and chronic bronchitis have shown cases with localized edema, hyperemia, hypersecretion and hyperesthesia of a bronchial segment, limited both above and below by apparently normal mucosa. Such lesions may be associated clinically with a wide variety of symptoms. Sometimes they may be associated with a more or less homogeneous density in the midlung. Retention of secretions may result in local pulmonary disturbances.—*Bronchite segmentaire*, E. Rist, P. Amerille & J. M. Lemoine, *Presse méd.*, March 15, 1947, 55: 173.—(E. Bogen)

Bronchial Spasm.—Wheezing may occur in cardiac asthma without the presence of basal râles; from the standpoint of physical signs, this wheezing may be indistinguishable from the râles of bronchial asthma. In most cases, studies of the circulation velocity of the blood will differentiate cardiac from bronchial asthma. Contrary to previous opinion, adrenalin will produce relief of symptoms in most cases of cardiac asthma with wheezing respiration; 0.5 cc. of adrenalin was injected subcutaneously in 9 patients with heart failure with sibilant râles and markedly prolonged circulation time. In each case, there was a definite increase in vital capacity; this increase averaged 510 cc. Inhalation of vaponofrin in 5 cases produced comparable results. All the patients felt much improved and there were no untoward results. In 11 patients with cardiac failure and basal râles, but no wheezing, adrenalin and vaponofrin produced little or no increase in vital capacity. Four patients of the first group were followed

until frank cardiac failure with basal râles supervened; at this time, wheezing disappeared and no relief was obtained by the use of adrenalin. In 5 normals, used as controls, adrenalin produced no change in vital capacity. Vital capacity is increased by venesection in patients with cardiac failure and, similarly, in normal people. The exact mechanism of the action of adrenalin in increasing the vital capacity of patients with cardiac asthma is not clear. The speed of the action suggests that the change occurs as a result of relief of bronchiolar spasm.—*Bronchial Spasm in Cardiac Asthma*, M. Plotz, *Ann. Int. Med.*, April, 1947, 26: 521.—(H. R. Nayer)

Lipid Pneumonia.—Changes in the lung produced by the introduction of oils have been a pitfall in diagnosis of chest diseases. A patient, 19, a member of the Women's Land Army, was admitted to the hospital on July 4, 1945, with an acute febrile illness resembling rheumatic fever with erythema nodosum. The chest was normal clinically; temperature was 100.2°; pulse 120 and respirations 22. The fauces were injected. There were raised red patches on the legs. An X-ray film of the chest showed a collapsed right middle lobe and enlarged mediastinal lymph nodes. Blood picture was normal, sputum negative. By exclusion, a diagnosis of Hodgkin's disease was made. Two courses of X-ray therapy were given. No change was produced. On April 30, 1946, patient was readmitted. She was dyspneic and had enlarged neck veins and shallow respirations. Percussion was dull, and there was bronchial breathing in both lungs. X-ray films showed an increased mediastinal shadow near the lung roots. She died May 12th. Necropsy findings showed the air passages acutely inflamed. The mediastinal lymph nodes were enlarged. The lungs were firm and solid. On gross section the upper lobes were infiltrated by a firm, pinkish material. Histological appearance of the lungs showed intense histiocytic activity throughout the alveoli. On frozen section, the macrophages

were seen to be distended with fat globules. On questioning her friends, no history of the use of an oil in nose drops or mouth spray could be elicited. This condition may be more common than is often supposed and should be considered in the differential diagnosis of chronic inflammation of the lungs.—*Lipoid Pneumonia: A Pitfall in Diagnosis*, R. E. Rewell, *Brit. M. J.*, March 29, 1947, 4499: 409.—(R. W. Clarke)

Industrial Lung Diseases.—Substances handled in industry may attack the respiratory tract and produce pneumoconioses, inflammatory and allergic conditions and possibly carcinoma. Cadmium, vanadium and beryllium are important constituents of certain alloys. The first two metals, if inhaled in the form of oxides in dust or fumes produce inflammation of the upper and lower respiratory tract, which may be acute or chronic. Acute bronchopneumonia, at times fatal, may follow poisoning with cadmium oxide, and chronic bronchitis is more often seen in vanadium workers. Beryllium fumes are of statistically greater importance because of the use of this metal in the aircraft industry. The upper respiratory tract is profoundly irritated, and the inflammation may extend into the lung producing bronchiolitis and chemical pneumonia. Autopsy of some fatal cases showed a picture of atypical pneumonia with hemorrhage and edema. The predominating cell infiltration consisted of plasma cells. [Some beryllium cases have an X-ray appearance very much like disseminated nodular sarcoidosis, the nodules being rather small. There is also some histological similarity.] Bagassosis is characterized by acute febrile illnesses in which cough and dyspnea are outstanding. The X-ray film shows scattered miliary densities. The picture is one of acute diffuse bronchiolitis. The majority of cases clear within weeks or months, but some have resulted in chronic fibrosis, bronchiolitis and bronchiectasis. One such autopsy is on record. The etiological agent in this disease is not known. Bagasse contains 1 to 2 per cent of amorphous silica, and

0.1 per cent of quartz, but the majority of the quartz particles are larger than those considered necessary for production of silicosis. It is believed that fungi may play an important part in breaking down bagasse fiber into a fine vegetable dust, and may render this toxic. The disease resembles byssinosis. In the past it was felt that the high incidence of carcinoma in the Schneeberg miners was due to the radioactivity of the hard rock. Recently it has been questioned if the high arsenic content of the rock, 0.45 per cent, may not be the cause of development of cancer. Arsenic may also be the carcinogenic agent in the nickel and copper mines of Sudbury, Canada. In the field of pneumoconiosis, silicosis is still the most important hazard. Recently there has been some tendency to ascribe a part in the pathogenesis of this disease to the accompanying anthracosis. Iron oxide, too, has been held to be rather harmless in the past and, while it is true that it does not produce fibrosis, it seems reasonable to assume that large accumulations of iron oxide in the lung would lead to some loss of elasticity and resulting functional impairment. These changes are observed in electric arc welders and to a lesser degree in oxacetylene welders. In boiler scalers, the pneumoconiosis appears to be due to a combination of the effects of silica and iron oxide. Treatment of these diseases belongs properly in the field of industrial hygiene and preventive medicine. Much has been accomplished by attention to good ventilation, dust control measures and the wearing of protective clothing and respirators. Whenever possible, silica containing dusts used in industry were substituted by harmless dusts. It should be the rule that no person under 18 years be employed on or within 20 feet of blasting apparatus.—*Industrial Medicine, D. Hunter, Schweiz. med. Wchschr., Sondernummer, September 16-21, 1946, 76: 917.*—(H. Marcus)

Phosgene Poisoning.—Six war-workers with acute exposure and 5 with chronic exposure to phosgene gas were studied for evidences of disturbance of pulmonary, circulatory and

psychic functions. The acute exposure, after the initial pulmonary edema subsided, produced rather marked symptoms, but without a consistent pattern of disturbed pulmonary function. Such changes as were found indicated beginning pulmonary emphysema. There was marked effect at the psychic level, with suggestive correlation with the severity of symptoms. The patients chronically exposed to smaller amounts of the gas, but for periods of one and one-half to three and one-half years had less marked symptoms but more constant evidence of impaired pulmonary function due to emphysema. Psychic factors were not prominent in this group. A curious but striking symptom in both groups was rapid shallow respiration, which could be altered at will, but persisted in sleep and during oxygen administration; it was attributed to a disturbed Hering-Breuer reflex.—*Study of the Residual Effect of Phosgene Poisoning in Human Subjects: I. After Acute Exposure. II. After Chronic Exposure, M. Galdston, J. A. Luetscher, Jr., W. T. Longcope & N. Ballick, with assistance of Virginia L. Kremer, G. L. Filley & J. L. Hopson, J. Clin. Investigation, March, 1947, 46: 145, 169.*—(A. A. Cohen)

Postoperative Atelectasis.—In order to determine the time interval between operation and roentgenographic appearance of atelectasis, roentgenograms of the chest were taken immediately, four and twenty-four hours after gastrectomy. Of 55 cases, 26 developed abnormal signs, consisting of increased markings or various stages of atelectasis. These were not confined to any particular age group. There was no difference in incidence between those with antecedent chest disease and those without. The first signs of atelectasis were noted in the four-hour film in 5 cases. By twenty-four hours, there was involvement in 13 cases. The changes consisted of patchy or lobular atelectasis. In all these cases, there were abnormal physical signs such as râles, rhonchi or occasional bronchial breathing. There was no mediastinal shift. In 10 other cases, there was an increase in the vascular markings in either the lower lobes or the

hilar regions. In 7 the changes were first seen at four hours; in the others, they were not noted until twenty-four hours. Some of the changes noted at four hours cleared up by twenty-four hours. Where atelectasis was first noted at twenty-four hours, increased vascular markings in the affected areas had been noted at four hours. In 3 other cases, the changes were those of bronchopneumonia or of collapse with effusion. A review of the results from the standpoint of timing showed at four hours patchy atelectasis in 5 cases and increased vascular markings in 7 cases. Of the latter, by twenty-four hours the changes had either disappeared, remained the same or progressed to atelectasis. At twenty-four hours, there were 6 more cases of atelectasis. It is concluded that the twenty-four-hour film is the most valuable single examination.—*Atelectasis after Partial Gastrectomy*, P. Springer, *Lancet*, March 8, 1947, 1: 289.—(A. G. Cohen)

Cancer of Lung.—In two and one-half years, the authors have seen 107 patients with cancer of the lungs. Of these, only 21 (21.4 per cent) presented no contraindications for an exploratory thoracotomy. This low percentage is attributed to the delay in making the correct diagnosis. Cancer of the lung is asymptomatic in its early stages. Its principal symptoms, in order of their frequency encountered, are: cough, loss of weight, expectoration, hemoptysis, fever and anorexia. Two types can be distinguished: peripheral cancer or cancer of a large bronchus, central cancer. Whereas the latter type is diagnosed by bronchoscopic biopsy, the former necessitates an early exploratory thoracotomy. Of 21 patients operated upon, only 6 had positive bronchoscopic findings. For the other 15 patients, the diagnosis was made, on the basis of suspicious X-ray findings, during thoracotomy. The operation of choice is pneumonectomy. A lobectomy is insufficient as the hilar lymph nodes cannot be completely removed. Clinical contraindications are: metastases in other organs, especially in the axillary or cervical nodes; paralysis of a vocal

cord; Horner's syndrome; paralysis of the diaphragm; hemothorax; cachexia. Bronchoscopic contraindications are: invasion of the trachea; widening of the angle of the bifurcation, which is a sign of invasion of the tracheobronchial nodes; general rigidity of the bifurcation and of the bronchial tree. Of the 21 thoracotomies, one case was lost during the operation from acute emphysema. Only 12 patients were benefited by a resection which reduces the operability in this series to 57.1 per cent (or 11.2 per cent of the entire series of 107). Eleven pneumonectomies and one left inferior lobectomy were done. Of those 12 patients, 3 died postoperatively. The lobectomy case showed brain metastases after one year and eight months. Nine patients are alive over a period of fifteen days to two years.—*Nuestra experiencia en el tratamiento quirurgico del cancer del pulmon*, O. J. Cames, A. Cesandli & F. E. Tricerri, *An. de cir.*, September, 1946, 11: 108.—(W. Swienty)

Carcinoma Emboli in Lung.—Definite thickening of the intima of smaller arteries and veins was often noticed during the histological examination of lungs of patients dying from carcinoma of various organs. This change was found in lungs disclosing no metastatic tumors as well as in those that did. These changes were more severe and much more frequent in carcinomatous patients than in patients of similar or older age groups without carcinoma. It has been known for many years that tumor emboli may occur in the lungs in the absence of metastasis; "tumor embolism is not metastasis." The present study is based on the histological examination of the lungs of 12 patients dying from carcinoma of various sources outside of the lungs. The ages of the patients varied from 36 to 60 years. Only those lungs were studied which histologically disclosed tumor emboli but no frank metastasis. These emboli were found in the smaller and smallest branches of the pulmonary artery, in capillaries, and in small pulmonary veins. A small sheath of fibrin and hyaline thrombi almost invariably were encountered adjacent to the tumor cells.

The thrombi seemingly caused atrophy of adjacent tumor cells which were gradually replaced by the growing thrombi. Eventually these thrombi became organized, but clumps of tumor cells were still recognizable either within the new channels or imbedded within the growing connective tissue. Thus, not the tumor emboli but the hyaline thrombus became organized and caused the disappearance of the tumor cells. When only mural thrombi were encountered, the eventual organization caused localized intimal thickening which very closely resembled pulmonary arteriosclerosis. (With 2 plates)—*The Fate of Carcinoma Emboli in the Lung*, O. Saphir, *Am. J. Path.*, March, 1947, 23: 245.—(J. S. Woolley)

Bronchial Adenoma.—Five cases illustrate the histological structure and characteristics of bronchial adenoma. In different tumors, and frequently in different areas of the same tumor, clear tumor cells resembling secretory cells of the bronchial glands and deep-staining round cells similar to the basal cell layer may predominate. Since the tumors have invasive tendencies and are potentially malignant, radical surgical removal rather than local resection through a bronchoscope, is advised.—*Five Types of So-called Bronchial Adenoma*, M. E. Sano & R. Meade, *Arch. Path.*, March, 1947, 43: 235.—(E. Bogen)

Hemangioma of Lung.—The condition is rare. Review of the French, American and English literature disclosed 5 cases. The author reports 2 cases in which the tumor was diagnosed clinically and removed surgically. The chief diagnostic features are: (1) non-specific cardio-respiratory symptoms, (2) cyanosis, (3) polycythemia and clubbing of fingers, (4) exocardiac murmurs in the chest, (5) telangiectases on skin, mucous membranes and other viscera and (6) irregular circinate opacities in chest roentgenograms. The

cyanosis is due to arterio-venous shunt. The telangiectases are most important in diagnosis; they are present chiefly on the face, lips and soft palate. The treatment is surgical resection; there is otherwise danger of severe hemorrhage.—*Cavernous Hemangioma of the Lung*, W. Whitaker, *Thorax*, March, 1947, 2: 58.—(A. G. Cohen)

Chorionepithelioma.—Although a chorionepithelioma is usually a highly malignant tumor, it at times may digress from the usual clinical course. Pulmonary metastases occur frequently, grow rapidly, and are an important factor in mortality. Regression and even disappearance of pulmonary metastases may follow removal of the primary tumor by surgery or radiation. The case of a 32-year-old woman with an isolated metastasis of such a tumor in the lung, for which a lobectomy was done, is reported. The patient after three years was in excellent health. The Aschheim-Zondek was positive the day before operation and negative the day following. A pan-hysterectomy performed a month after lobectomy failed to reveal any evidence of disease of the pelvis.—*Metastatic Chorionepithelioma of the Lung Treated by Lobectomy*, H. C. Maier & H. C. Taylor, Jr., *Am. J. Obst. & Gynec.*, April, 1947, 53: 674.—(R. W. Clarke)

Thoracoscopy in Chest Wounds.—In all penetrating wounds in the chest when pneumothorax or hemopneumothorax develops, thoracoscopy will furnish valuable information on the extent of the injury, intrapleural hemorrhage, the involvement of the lung, etc. It will also permit the removal of blood and often obviate the need of an exploratory thoracotomy. Five cases are described to illustrate the value of the method.—*A toracosopia como método de exploração nas feridas pendrantes do tórax*, J. M. Castello Branco, *Clín. fisiol.*, July-September, 1946, 1: 229.—(A. A. Moll)

LATE PRIMARY INFECTION AND BCG VACCINATION¹

HAQVIN MALMROS

In spite of the extraordinary decline in the tuberculous death rate over the past century we still have a number of problems to solve before reaching a point where the war against tuberculosis can be regarded as won. The incidence of infection, as evidenced by the tuberculin test, has declined year by year. At present it may be assumed that in large parts of the world most of the rural population reach adolescence without having been infected by tuberculosis. Even in the cities it is not uncommon to meet young people who are negative to tuberculin. The time is, however, still distant when tuberculosis will become so rare a disease that there is no considerable risk of infection. For the present it must be expected that sooner or later practically every individual will be exposed to tuberculous infection. To get a complete picture of the tuberculous infection in a community, preferably the whole population should be tuberculin tested. This has been done in the city of Örebro in Sweden, where the whole population—about 50,000—was tuberculin tested in 1944 (see graph 1).

The course of the tuberculin-reactor curves for different cities may obviously vary. In essentials, however, they will probably show the same thing, that is, a greater or smaller number of tuberculin-negative children and young people, but few or no tuberculin-negative adults in the older age classes. The rural population, too, becomes infected to almost 100 per cent, at any rate in such areas as have lively communications, though, as a rule, the infection occurs here much later than in the cities. Hence we must now expect primary tuberculous infections in adults to a very great extent.

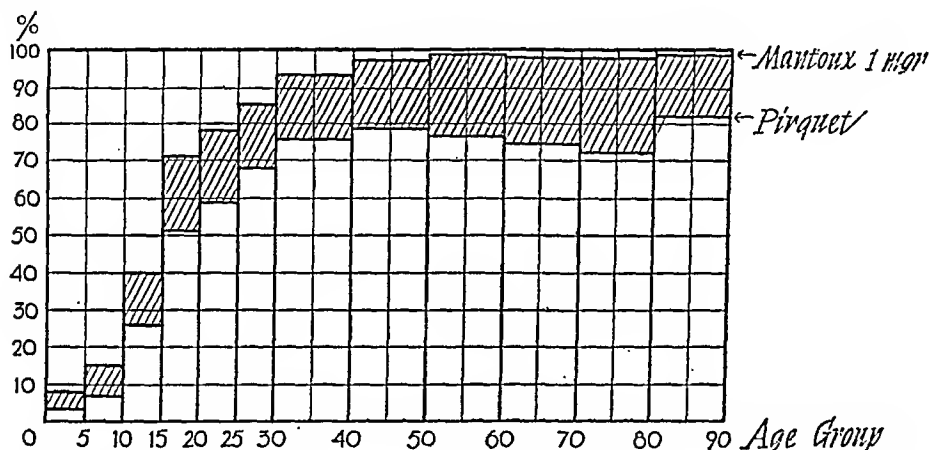
PRIMARY INFECTION OR REINFECTION IN ADULTS

What significance has such a primary infection? Even in the modern literature we find, at least apparently, quite different views on this important question. Especially Scandinavian authors claim that primary infection in adults may have serious consequences, since they believe that pulmonary tuberculosis of adults is often a sequel to late primary infection (Heimbeck (1), Arborelius (2), Kristenson (3), Malmros and Hedvall (4) *et al.*). In the American literature dealing with the subject, on the other hand, it is frequently held that primary infection is not dangerous. Myers (5) urges this view most emphatically. In the 1946 edition of *Tuberculosis among Children and Young Adults*, he writes, "We have learned through the study of students of nursing and medicine that adults who have escaped tubercle bacilli through infancy and childhood develop a very benign primary tuberculosis if they become infected in adult life" . . . "The first infection type of tuberculosis is a benign form of disease, rarely causes significant symptoms and in our experience has never caused death." It should be noted that Myers is not referring to tuberculous infection as a whole, with

¹ From the Central Hospital of Örebro, Sweden.

all its consequences, but only to the first manifestation of the disease, the primary complex itself. What follows the primary lesion is termed "reinfection" by him. Under this term he comprises tuberculous meningitis, pleuritis and "true" pulmonary tuberculosis. Quite naturally, the prognosis of these types of tuberculosis is entirely different. Myers himself states that the "reinfection type" of pulmonary tuberculosis among young adults is the first cause of death [except for accidents] in the United States for this age group.

It may be queried whether it is suitable or even possible to discriminate sharply between primary infection and so-called reinfection. On different occasions Myers compares tuberculous infection with syphilis. Let us extend this parallel. To state that a primary infection type of tuberculosis has a good prognosis is comparable to stating that a primary syphilitic lesion is a harmless symptom of disease. It is certainly quite correct that a primary syphilitic lesion usually



GRAPH 1. A tuberculin survey of the whole population (about 50,000) in the city of Örebro, Sweden, in 1944.

produces insignificant symptoms and probably never terminates in death, but it is the subsequent course that is decisive for the prognosis. Spirochetes are spread from the primary lesion and may later give rise to serious symptoms. The disease often lies latent for a considerable time and can only be demonstrated by serological tests. As long as the disease has not healed the body is not susceptible to reinfection. Hence actual superinfection does not occur in syphilis.

So far as tuberculous infection is concerned the term "reinfection," as is known, has unfortunately been considerably abused. As Terplan (6) has clearly pointed out, reinfection signifies a new infection with tubercle bacilli from without and excludes any formal genetic relationship to the primary infection. The occasionally employed term "endogenous reinfection" ought to be completely abandoned, since it is a *contradictio in adjecto*. Instead, a tuberculous process caused by bacilli derived from older tuberculous lesions should be denoted as an endogenous exacerbation.

Whether a true reinfection or an endogenous exacerbation is present in a given case is no doubt extremely difficult to decide. In such circumstances it would

THE UNIVERSITY OF CHICAGO
DIVISION OF THE PHYSICAL SCIENCES
DEPARTMENT OF CHEMISTRY
JANUARY 1954
MEMORANDUM FOR THE RECORD
SUBJECT: [Illegible]
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of how often a progressive pulmonary tuberculosis starts directly from a primary complex. It is clear that this occurs, but in Hedvall's large and well examined material only some 10 such cases could be detected. Hence it seems as though an acute tuberculosis showing rapid progression from the primary complex is commoner in Norway. This may be because Frostad's investigation was carried out during the war, when the nutritional condition was far from good. Thus, even if direct progression from the primary lesion is a relatively rare development under ordinary circumstances, it is nevertheless by no means uncommon for a progressive pulmonary tuberculosis to develop in close association with the primary infection. As was stated above, this development generally occurs from small multiple apical foci ("subprimary initial foci"), which can often be detected as early as a few months after the primary infection. If large groups of a population are systematically tuberculin tested at frequent intervals and simultaneously X-rayed, it is found that a primary infection in adults not infrequently leads to a progressive pulmonary tuberculosis. In reality, it is probable that progressive pulmonary tuberculosis nowadays is more often due to a primary infection in adult age than to an infection contracted in childhood. There are also, of course, cases in which a latent infection lights up after several years. In general, however, progressive pulmonary tuberculosis develops in close conjunction with primary infection. Törnell (10), for instance, has shown that, among the patients admitted to a large sanatorium for pulmonary tuberculosis, probably over 60 per cent consisted of cases which had recently undergone a primary infection.

IMMUNIZATION WITH BCG

The view that the majority of cases of pulmonary tuberculosis are a direct consequence of late primary infection has been accepted more and more in the Scandinavian countries. This determines, to a high degree, the preventive tuberculosis campaign in these countries. If most cases of pulmonary tuberculosis are to be expected among those primarily infected in adult age, the logical consequence must be that service in a tuberculosis department involves a considerable danger for tuberculin-negative medical and nursing hospital personnel. Indeed, numerous investigations have shown that exposure to tuberculosis implies a substantial occupational hazard. As far back as 1927, Heimbeck (11) showed that the risk was particularly great for the nonreactors to tuberculin. He therefore suggested immunization of nonreactors with BCG. Since Wallgren (12) found that reliable immunization could be produced without abscess formation by intracutaneous injection of BCG vaccine, this method has been employed to a wide extent in Scandinavia.

In Sweden all medical students and pupil nurses are now tuberculin tested before beginning hospital service, and the nonreactors are vaccinated. Conscripts in the Services are vaccinated at the beginning of their term of service, and so are the majority of school children in the last class of the primary school before their final examinations.

Still more extensive vaccinations have been performed within certain dis-

tricts. In the city of Örebro, for instance, the whole population has been tuberculin tested, and the nonreactors have been vaccinated with BCG. All newborn babies are also vaccinated. The children continue to be under supervision at the child welfare centres and in the schools. If in the course of the repeated tuberculin tests it is found that the reaction has again become negative, vaccination is repeated. However, as is evident from Ryden's (13) investigations, the positive tuberculin reaction persists for rather a long time, even when BCG vaccination is carried out just after birth. Thus, it was found that 93 per cent of those vaccinated and converted were still tuberculin-positive two to three years after the vaccination. Intracutaneous vaccination, according to Wallgren, had been used in these tests. Birkhaug's needle puncture method with a twenty times stronger vaccine was tested in a small number of cases, but the result was not satisfactory. For instance, of 282 newborn children vaccinated by Birkhaug's method, only 57 per cent were tuberculin-positive on being tested seven to eight weeks afterwards. On the other hand, of 4,343 newborn infants vaccinated with 0.05 mg. of BCG by Wallgren's intracutaneous method, over 90 per cent reacted to tuberculin when tested after seven weeks.

During the years 1942 to 1946, about 18,000 BCG vaccinations were carried out in the Örebro district under the author's supervision. No complications of any serious nature occurred. Four cases of erythema nodosum appeared a few weeks after vaccination, but these symptoms rapidly receded and the subjects have subsequently exhibited no sign of active tuberculosis. It is, of course, quite possible that in these cases erythema nodosum was due to something else, for example, a streptococcal infection. In some 10 cases a relatively large abscess developed at the point of inoculation, which in all instances gradually healed by cicatrization but without other persisting detriment. The cause of these abscess formations was probably a defective technique, the vaccine being injected subcutaneously instead of intracutaneously. Earlier, as is known, the subcutaneous method of vaccination was used at some stations, and, then, large abscesses were frequent. If the injection is carefully carried out intracutaneously, abscess formation hardly ever occurs. In most cases only an infiltrate the size of a pea to a finger-tip is formed, and this is gradually absorbed.

PREPARATION OF VACCINE AND SAFETY CONTROLS

All BCG vaccine used in Sweden during the past years has been prepared in a single laboratory² and under Dr. A. Wassén's constant supervision.

In a personal communication, Doctor Wassén has given the following information about the preparation of the vaccine. The strain employed for the preparation of the Swedish BCG vaccine was obtained in 1926 from the Pasteur Institute in Paris and has since been kept "active" continuously. In the cultivation of BCG bacilli as well as the preparation of the vaccine the directions given in *Technique des Cultures de B.C.G.* by Calmette and Guérin are followed in all essentials.

The bacilli are first cultured for a fortnight on potato bile, then for a fortnight in potato glycerin, thereupon for eleven days on Sauton's medium I, and finally for eleven

² The Bacteriological Laboratory at the Sahlgren Hospital in Gothenburg, Sweden.

days on Sauton II. A constant temperature of 38.3° C. is maintained in the thermostat. Hence the age of the culture used for the vaccine is eleven days. Calmette recommended a growth-period of twenty to twenty-five days. It has been found, however, that vaccine from such old cultures yields many negative results, probably because many of the bacilli are dead. With the use of young cultures the results have improved without any increased toxicity. The bacilli are collected, filtered, pressed dry and weighed. Thereupon the compressed bacilli are transferred to a retort containing stainless steel balls, which are rotated for eight minutes. A diluent is then added so that the vaccine, when ready, contains 0.5 mg. of bacilli per cc. Before being issued the vaccine is tested for non-virulence by inoculation on guinea pigs. In addition, careful bacteriological tests are made to be sure that it does not contain other bacteria. The laboratory has issued vaccine in constantly increasing quantities since 1926. During the year 1945 vaccine was prepared for over one million vaccinations. In not a single case has it been possible to demonstrate that the attenuated BCG strain has regained its virulence.

The harmlessness of BCG is, accordingly, established beyond all doubt, but quite naturally minute control and constant supervision must be demanded of the bacteriological laboratory that prepares the vaccine. No other culture of tubercle bacilli and no tuberculous material should be allowed to enter the laboratory in which this vaccine is produced. In this connection it should be mentioned that the Lübeck disaster of 1930 was not caused by the BCG strain used having regained its virulence, but by the use, by mistake or intention, of another, virulent tubercle bacillus strain. Thus, there is no justifiable reason for citing this tragic event as an argument in favor of the possibility that BCG may regain its virulence, although theoretically this possibility can, of course, not be entirely dismissed. However, experience with millions of vaccinations during many years shows that in practice such a possibility need not be entertained.

HYPERSENSITIVITY AND ACQUIRED RESISTANCE

Even though the BCG vaccine itself is completely harmless, the question remains whether it can do harm by producing a hypersensitivity that manifests itself as, for example, a positive tuberculin reaction. Myers (5) considers that BCG vaccination involves a considerable risk because it produces tissue hypersensitivity. It is, of course, correct that sensitiveness of the tissues may be a dangerous factor in the development of clinical tuberculosis. This is more so, especially when the body already contains an active focus with millions of highly virulent tubercle bacilli. If these bacilli come in contact with hypersensitized tissue, for example in the lungs, a violent reaction may follow. A quite different state of things exists, however, if the sensitization has been produced by greatly attenuated BCG bacilli. There is, then, no focus containing virulent bacilli within the body, and virulent bacilli can only come from outside sources. Even if the subject lives in a tuberculous environment, probably only relatively few virulent bacilli will, as a rule, be inhaled. The sensitiveness to tuberculin induced by BCG vaccination certainly implies a sensitization, but if the number of inhaled bacilli is small the body reaction to them can hardly become so violent

that it is deleterious. As is known, some authors even hold it probable that hypersensitivity is an important mechanism of acquired resistance. This is not definitely proved and there are some things which suggest that acquired resistance can be established without the concomitant development of hypersensitivity. However, there is nowadays scarcely any reason to warn against the use of BCG vaccination on the ground of theoretical speculations. As Rich (14) expresses it, dogmatic generalizations long obscured unsolved problems relating to hypersensitivity. Practical experience from many thousands of BCG vaccinations has shown that those vaccinated do not by any means fall ill with malignant forms of pulmonary tuberculosis if they are subsequently exposed to tuberculous infection. On the contrary, the great majority resists such an infection without exhibiting any morbid symptoms whatever. This applies to adults as well as to children. The resistance acquired through vaccination is evidently so strong that it affords an effective protection.

EFFICACY OF BCG VACCINATION

The author's material now comprises over 18,000 persons vaccinated during the years 1942 to 1946. Over one-fourth of the cases consists of newborn babies; 6,100 had attained the age of 15 years at the time of vaccination. The examinations were carried out within a geographically well circumscribed area having a population of 230,000. Within the district there are two tuberculosis sanatoria, one central hospital with medical and pediatric departments and some smaller hospitals. As soon as a case has been admitted to any hospital under the diagnosis of tuberculosis or suspected tuberculosis, it is ascertained whether the patient has been previously BCG vaccinated. By this means it has been possible to check whether any of those vaccinated have contracted tuberculosis. During the period 1942 to 1946 only 3 cases of suspected tuberculosis were reported among the 18,000 vaccinated.

Twelve months after vaccination, a boy, one year old, fell ill with symptoms that were interpreted at first as evidence of tuberculous meningitis. At autopsy, however, it was found to be a cerebral tumor and no tuberculosis could be found.

A housewife, 26 years old, developed erythema nodosum one and one-half years after BCG vaccination. Roentgenological examination revealed considerably enlarged hilar lymph nodes, and she was, therefore, transferred to a sanatorium. On closer examination, it was found that the patient was negative to tuberculin (3 mg. OT). She had earlier been tuberculin-positive after the BCG vaccination but had again become negative. As this change from positive to negative reaction occurred at the same time as the patient developed erythema nodosum and enlarged hilar lymph nodes, the diagnosis was made of *lymphogranulomatosis benigna* (sarcoidosis). The subsequent course also argued in favor of this diagnosis. No evidence of tuberculosis could be discovered.

A probational nurse, aged 22, was BCG vaccinated before starting her hospital duties in 1943. A tuberculin test one month later showed that she reacted very slightly to tuberculin. In 1944 the tuberculin reaction was checked and found to be negative, and therefore she was again BCG vaccinated. After this inoculation the tuberculin reaction

was distinctly positive. At a control at the end of 1945, just before she was to begin service at a tuberculosis sanatorium, another tuberculin test did not cause a definitely positive reaction. However, on account of shortage of personnel she was allowed to start work there in spite of her negative tuberculin reaction. X-ray films showed no pulmonary changes. Two months later it was found that she had become a strong reactor. Another X-ray film showed normal conditions. Some months later, however, she developed pleurisy with effusion. X-ray examination disclosed no parenchymal lesions. No tubercle bacilli could be demonstrated on culture and inoculation of pleural fluid. Nonetheless the case must be interpreted as tuberculosis, the hitherto only known one among the 18,000 persons vaccinated. It is obvious that in this case the vaccination had not given sufficient resistance. This may depend on a faulty technique or on deficient ability to react, since, despite two vaccinations, the patient had become only temporarily tuberculin-positive. In the great majority of cases the tuberculin reaction has been distinctly positive after the vaccination and the reaction has remained positive for several years. The case under consideration shows the importance of tuberculin-testing of BCG vaccinated hospital staffs. Only definitely tuberculin-positive persons should be permitted to work in hospital wards where the risk of infection is specially great.

The material presented here is rather large, but the time of observation is too short to allow any safe conclusions as to the efficacy of BCG vaccination. That this vaccination affords a good protection is evident from other investigations in which a comparatively large control material has been available.

Hyge (15), in 1943, observed an epidemic of tuberculosis at a girls' school in Denmark. These observations led to very definite conclusions as to the protection that BCG vaccination affords against tuberculous infection. Of 105 Mantoux-negative pupils, aged from 12 to 18 years, of whom only 94 had probably been exposed to infection, 70 became tuberculin-positive. Of these primarily infected, 41 presented distinct X-ray changes, and in 37 cases tubercle bacilli could be demonstrated on culture of the stomach contents. The great majority of the cases recovered, but 6 developed a progressive pulmonary tuberculosis, and one of these died. There were at the school, at the same time, 133 pupils who had been BCG vaccinated a few months earlier and had become tuberculin reactors. Probably only 106 of these were exposed to the source of infection which was later discovered. Among these 106 there were only 2 cases that showed tuberculosis. In both cases a pulmonary tuberculosis developed with cavities that required pneumothorax treatment. Among the 130 who were originally (spontaneously) tuberculin-positive, of whom probably only 105 were exposed to infection, 4 cases of pulmonary tuberculosis occurred, all mild.

Aronson and Palmer's (16) recently published report on BCG vaccination among North American Indians likewise allows very definite conclusions in regard to the efficacy of BCG vaccination. The report is based on a study of 3,007 Indians, ranging in age from one to 20, inclusive; 1,550 of whom were vaccinated. The remaining 1,457, who were likewise tuberculin-negative, served as controls. During the six-year period covered by this investigation, 28 tuberculosis deaths occurred among the controls, as compared with only 4 such deaths

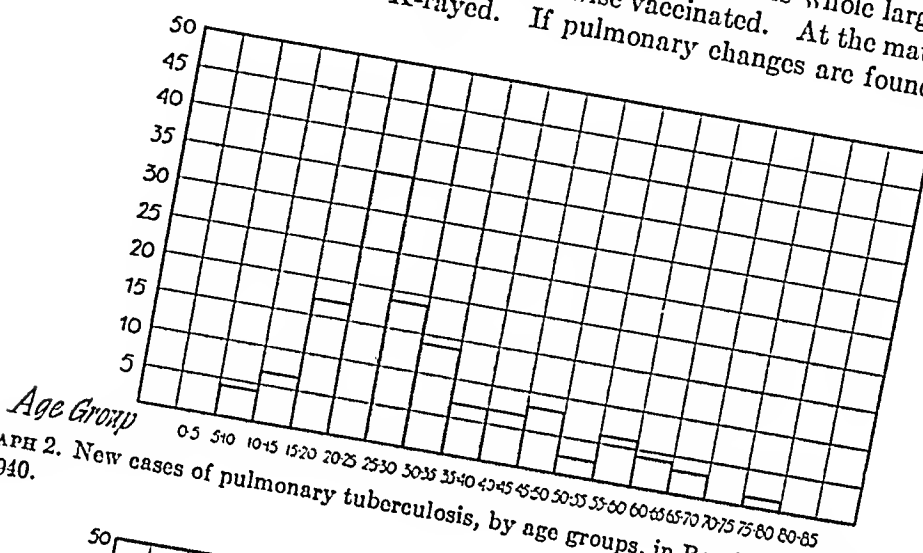
among the vaccinated group. Including those who died from tuberculosis, 48 were classified as having advanced pulmonary lesions or extrapulmonary tuberculosis among the controls and 9 in the vaccinated group. There were 20 patients with X-ray evidence of minimal lesions among the controls and 8 among the vaccinated. The corresponding figures for cases exhibiting enlarged hilar lymph nodes were 99 and 19, respectively, and for pleural effusion 18 and 4, respectively. Comparison of all types and deaths showed 185 among the controls and 40 in the vaccinated group.

A TUBERCULOSIS CONTROL PROGRAM

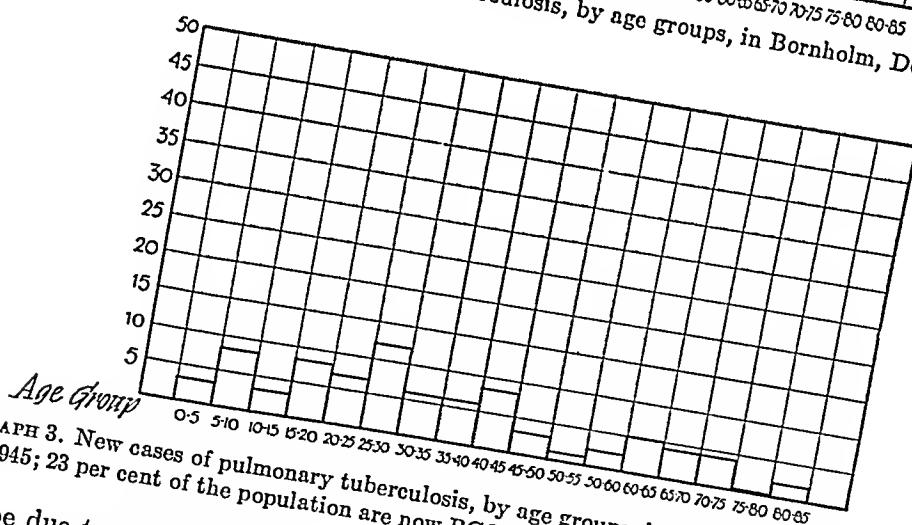
In a recently published paper, Myers (17) has given an account of the tuberculosis control program of the city of Minneapolis as it was developed during the past twenty-five years. He also discussed the plans for the future. The results have been good: there has been a steady decrease in the mortality rate and a decrease in the infection attack rate. The main principle underlying the program adopted in Minneapolis has been to trace cases of infectious tuberculosis and to isolate them in hospitals and sanatoria. This is, of course, a method that ought to be applied to the greatest possible extent to minimize the risk of infection for the whole population. It is, however, doubtful whether these measures alone will lead to the ultimate goal—eradication of tuberculosis. When faced with the figures from the school epidemic described by Hyge we cannot shut our eyes to the fact that it involves a great risk to be tuberculin-negative when exposed to tuberculosis. For the time being, we must count upon the widespread risk of exposure. Students of nursing and medicine are especially exposed and will sooner or later probably become infected, even if an efficient contagious-disease technique is adopted during the hospital training course. A medical officer or nurse can hardly refuse to attend a tuberculous patient on the ground of being tuberculin-negative. Even if the infection attack rate is exceptionally low in Minneapolis, it is doubtless considerably higher in many other places. Every tuberculin-negative youth who undertakes a journey to a large city can, at the present risk, become infected with tuberculosis. As it has been proved that a late primary infection often leads to progressive pulmonary tuberculosis, we ought to try to protect young people in all possible ways. The best method at present known is to BCG vaccinate all nonreactors. If this method is employed among the whole population, it gives good results, as is evident, among other things, from the large-scale examinations carried out on the small Danish island of Bornholm, where 23 per cent of the population are at present vaccinated. As is shown in graphs 2 and 3, the number of recognized new cases of tuberculosis in the age groups 15 to 35 has diminished considerably since BCG vaccination was started on a large scale.

Within the district in which the present author operates, the following tuberculosis control program is now being applied. All inhabitants are completely examined by a mobile tuberculosis control unit, which goes its rounds from place to place within the district. This examination includes miniature photo-fluorography (70 mm.) of all adults and children over 14 years of age, tuberculin-

testing of the whole population and BCG vaccination of all nonreactors. The examination is voluntary, but every effort is made to obtain 100 per cent coöperation. Each person examined has to pay a fee of one Swedish krona (equivalent to about 25 cents). These fees almost suffice to finance this whole large-scale examination. All newborn children are likewise vaccinated. At the maternity departments all mothers are X-rayed. If pulmonary changes are found that



GRAPH 2. New cases of pulmonary tuberculosis, by age groups, in Bornholm, Denmark 1936-1940.



GRAPH 3. New cases of pulmonary tuberculosis, by age groups, in Bornholm, Denmark, 1941-1945; 23 per cent of the population are now BCG vaccinated.

may be due to active pulmonary tuberculosis, the child is isolated from the mother until the BCG vaccination has had time "to take." Children in the first and last classes of the primary schools, students of nursing, conscripts in the Services and other young people who are considered to be specially exposed to infection are tuberculin-tested. If their tuberculin reaction is negative again, another BCG vaccination is done. All new admissions to general hospitals are examined by miniature photofluorography. In addition, an endeavor is made

to utilize available X-ray appliances for the large-scale investigation. For instance, mass chest radiography is planned for visitors to a large exhibition that is to be held this summer. Such an examination can readily be carried out, as it has been found that clothed subjects can very well be examined by miniature photofluorography.

SUMMARY AND CONCLUSIONS

1. Late primary infection is a common cause of progressive pulmonary tuberculosis in young people and adults.
2. The frequently employed terms "reinfection" and "reinfection type" are misleading and should be abandoned.
3. Experiences from an extensive series of investigations and from a school epidemic suggest that nonreactors are specially exposed to the risk of contracting serious tuberculosis if they become infected.
4. BCG vaccination is harmless and gives good protection, and this method should therefore be used to as great an extent as possible.
5. Under no circumstances should students of nursing and medicine be allowed to perform duties at hospitals if they are tuberculin-negative. Only such hospitals as exert scrupulous tuberculosis control, including BCG vaccination of all nonreactors to tuberculin at least six weeks prior to the beginning of their service, should be accepted as training hospitals.
6. A modern tuberculosis control program should include miniature photofluorography of all adults and children over 14 years of age, tuberculin-testing of the whole population, with BCG vaccination of all nonreactors. By means of follow-up examinations it should be checked that the vaccinated persons remain tuberculin-positive. Should the tuberculin reaction again become negative, revaccination ought to be done.

SUMARIO Y CONCLUSIONES

Infección Primaria Tardía y Vacunación con BCG

1. La infección primaria tardía es causa frecuente de tuberculosis pulmonar evolutiva en los jóvenes y adultos.
2. Los términos tan empleados de "reinfección" y "tipo reinfección" se prestan a confusión y deben abandonarse.
3. Las observaciones derivadas de una extensa serie de investigaciones y de una epidemia escolar indican que los no reactivos corren sobre todo el riesgo de contraer una tuberculosis grave si se infectan.
4. La vacunación con BCG es inocua y proporciona buena protección, por lo cual debe ser usada en el mayor grado posible.
5. Bajo ninguna circunstancia debe permitirse que estudiantes de medicina y enfermería trabajen en los hospitales si son tuberculino-negativos. Como hospitales de adiestramiento debe aceptarse únicamente a las instituciones que ejerzan escrupulosa fiscalización antituberculosa, comprendiendo vacunación con BCG de todos los que no reaccionen a la tuberculina, por lo menos seis semanas antes de comenzar a prestar sus servicios.

6. Una moderna obra de lucha antituberculosa debe comprender fotorroentgenografías en miniatura de todas las personas adultas y niños de más de 14 años, comprobación con tuberculina de toda la población, y vacunación con BCG de todos los negativos. Por medio de exámenes periódicos debe comprobarse si los vacunados continúan siendo tuberculino-positivos. Si la reacción a la tuberculina se negativa de nuevo, hay que revacunar al individuo.

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BRONCHIAL LAVAGE FOR BRONCHIECTASIS

A Preliminary Report of a Simplified Technique

IAN P. STEVENSON¹

The current treatments of bronchiectasis leave so much to be desired that any method which promises relief to the victims of this disease deserves serious consideration. The medical management of bronchiectasis has certainly improved since the advent of the sulfonamides and penicillin, but because these drugs have no influence on the drainage of the bronchi, their effectiveness when used alone is restricted. By means of bronchial lavage it is possible to improve the drainage of the bronchi and afford the antibacterial drugs a greatly enhanced opportunity for success.

Bronchial lavage and the direct application of medications to the bronchial tubes has been advocated and sporadically practiced since Green (1) first wrote about it in 1855. As a diagnostic procedure, particularly in identification of tuberculosis and cancer of the lung, bronchial lavage has had many proponents. As a therapeutic measure its disadvantages for prolonged use have always seemed to offset its advantages, except in the hands of a few skilled physicians who have enjoyed great success with the method. To Mandelbaum (2) and Stitt (3, 4) belongs chief credit for establishing the technique of bronchial catheterization as a therapeutic measure. Others (5) have largely confirmed the methods and results of these two pioneers.

The earlier procedures for bronchial lavage have all involved catheterization of the larynx before lavage is carried out. This is a rather complex technique requiring considerable dexterity on the part of the physician and an equal amount of enthusiasm and self-control on the part of the patient. It usually involves the use of considerable local anesthetic and always necessitates the presence of the doctor since it is not feasible for the patient to carry out this procedure on himself at home. Under the circumstances it is not surprising that this method has never gained wide acceptance.

In 1945, Moore and Thompson (6) reported excellent results in one case in which a simplified technique was employed and the lavage performed by the patient himself. The present author has further simplified the technique so that it can be done at home by the patient. These modifications together with direct instillation of penicillin solution into the lungs after lavage have made this method of treatment worthy of more wide-spread trial. It need hardly be said that the application of penicillin to the bronchi after removal of the secretions is superior to merely coating the pooled secretions with inhaled penicillin dust or droplets.

¹Fellow in Internal Medicine, Alton Ochsner Medical Foundation, New Orleans.
Present address: Department of Medicine, Cornell University Medical College, New York, New York.

TECHNIQUE

Physiological saline solution can be used for lavaging, but Stitt and the present author have not found it as satisfactory as Bledsoe-Fischer solution (7). The latter is a modified Ringer's solution which is somewhat hypertonic and tends to have a dehydrating effect on the cells and prevents them from swelling. A strong stock solution is first prepared; this is composed of:

Sodium chloride	263.7 g.
Potassium chloride.....	10.6 g.
Calcium chloride (desiccated).....	21.0 g.
Distilled water q.s. ad.....	1000.0 cc.

Twenty to 22 cc. of this stock solution is then added to 500 cc. of distilled water to make the final Bledsoe-Fischer solution which is used in the lavage. This is itself cleansing when applied to the bronchial mucous membranes and its use alone without any antibacterial drugs has produced pronounced amelioration of symptoms.

The only supplies needed are a 20 or 30 cc. glass syringe fitted to a tracheal cannula, a one-ounce measuring glass for mixing penicillin solutions and a spray syringe for local anesthesia. In addition, some means of sterilizing the first three pieces of equipment must be available. This can be done either by placing them in a small catheter tray and boiling them or by the use of a small home sterilizer.

(1) *Anesthesia*: Local anesthesia is best accomplished by the use of a weak solution of pontocaine. At first, because of the sensitivity and natural anxiety of the patient, it is necessary to anesthetize the posterior pharynx and larynx thoroughly with a 1 or 2 per cent solution of pontocaine applied by spray and on applicators just as for a bronchogram. During the first few treatments it is advisable to instill about 1 cc. of the solution between the vocal cords into the bronchi. It is better at first to err a little on the side of completeness in giving the anesthetic; the patient may complain of the lump in his throat but, if he obtains satisfactory results from the procedure, he will not object to this. As experience is gained and as the patient becomes more accustomed to the procedure, less and less anesthesia is necessary. Finally, it may be sufficient to spray the larynx a few times with a 1 per cent solution of pontocaine administered through an atomizer² which is used with the tip directed downwards into the larynx. If this is done, no lump will be felt in the throat but, if a few minutes are allowed to elapse before the lavage is begun, the experienced patient will find the anesthesia quite adequate. He is able to swallow and taste without difficulty immediately after the lavage. Some patients have been able to dispense with anesthesia completely. Less anesthetic is necessary if the solution is gently warmed before being instilled.

(2) *Lavage*: As soon as anesthesia is complete, the solution is allowed to run onto the larynx from the tracheal cannula, the tip of which is held just above the epiglottis. The speed of delivery of the solution will depend upon the patient; some take it best when given rapidly, whereas others prefer to take it rather slowly and perhaps only during inspiration. Sometimes involuntary coughing interrupts instillation of the fluid and this is a sign of inadequate anesthesia or excessive rapidity of administration. However, familiarity on the part of the patient simplifies matters greatly and he soon learns to control his cough until all the solution has been taken. After about 20 to 30 cc. of the solution has been allowed to run in, the patient simply coughs up the solution and the secretions are raised freely with it. If desired and tolerated, more of the solution may be used at one

²de Vilbiss atomizer spray No. 127.

time before the patient coughs. The lavage is then repeated two or three times. As the patient becomes more accustomed to the procedure, he can tilt his trunk into various positions so that the fluid reaches different affected bronchi. Indeed, this posturing may be of the utmost importance in patients with lesions of the upper and middle lobes and, even if only the lower lobes are involved, it should be given careful attention. The patient can also learn to take deep inspirations as the fluid flows in so that it will reach the more dependent bronchi. At first, he may feel that he has not expelled all the solution and this may well be the case. Some of it undoubtedly is scattered throughout the lungs and absorbed there; but as the patient becomes more expert, his coughing will be more efficient. Further, it will often be possible as experience is gained to decrease the amount of solution used in each lavage without impairing the effectiveness of the treatment. In any case failure to cough up all the instilled fluid is not harmful, although there may sometimes be transient discomfort from this. If the patient bends forward and lowers his head, he can usually get rid of secretions which might otherwise be retained in the dependent bronchi.

MEDICATION

After the last lavage a medicated solution is instilled and allowed to remain briefly before being expelled. The medication should be instilled before the larynx becomes irritated as it sometimes will if there is much coughing. This laryngeal irritation is more common with the catheterizing procedure than with the one described here. If it occurs, further anesthesia is necessary before any more solution can be instilled.

Many different medicaments have been tried but none was of great value until the appearance of the sulfonamides. More recently, penicillin has largely superseded even these. Before treatment is begun, it is advisable to determine the bacteria involved since they may be more vulnerable to other drugs, such as streptomycin, than to penicillin. If penicillin is used, approximately 20,000 units are dissolved in 20 to 30 cc. of the Bledsoe-Fischer solution and the resulting solution is instilled as before. Stronger solutions are apt to foam; they are slightly irritating to the bronchi and they are no more effective. Stitt felt that the sulfonamide solutions he used should be retained for as long as an hour before being expectorated. This can be done but it is not easy or pleasant to control the cough reflex provoked by 30 cc. of fluid in the lungs. It does not appear to be necessary with penicillin solutions, which seem to be effective even when most of the solution is coughed out a few minutes after administration. In starting treatment the solution should be retained for longer periods and our patients are advised to retain the solution until they become uncomfortable, but not to suppress a natural cough which would eliminate some of it. Later, it may be coughed out much sooner.

REACTIONS

At first, with complete anesthesia and the novelty of the experience, this procedure is rather an ordeal for the patient and he may well wish to rest for a half hour or so before doing anything else. Some patients will require a little sedation before the lavage is given. Later, as experience increases proficiency, the

whole procedure becomes greatly simplified; it may take no more than a few minutes and seems little more than a deep gargle.

There are a few specific reactions which may be encountered and it is well for the physician to be aware of them and in certain instances to warn patients of their possibility. Such reactions are uncommon when viewed statistically, but to the individual patient they can be alarming and, if improperly handled, may turn him from continuance of the treatment. Nor must it be inferred from this discussion of reactions that any of them are serious as indeed they are not. Stitt (4), who has had a much more extensive experience with this treatment than the present author, has never encountered a case in which this procedure resulted in any harm or in extension of infection. The infection is much more likely to spread if retained secretions accumulate in the bronchi than if they are washed out by this procedure.

(1) *Immediate reaction from pontocaine:* This usually results from the use of excessive pontocaine but may be encountered in those who are sensitive to this drug in minute doses. It should be less frequent with this procedure than that of catheterization since less anesthetic is needed. It will be less common also if a 1 per cent solution is used instead of a 2 per cent solution. And it is naturally most likely to occur on the first few occasions when it is particularly desirable to have the patient well anesthetized in order to assure success. Later, as less and less anesthesia is required, such reactions are not encountered at all. The pontocaine reaction consists usually of nervousness, palpitations, tachycardia, sweating, faintness and dizziness. It may sometimes be difficult to distinguish these reactions from the natural nervousness of the patient when faced with this new procedure. On the first few occasions it may be helpful to sedate nervous patients slightly before the lavage. Each patient should be interrogated for a history of sensitivity to drugs such as pontocaine and cocaine. The treatment of mild reactions is unnecessary; nor do these preclude continuing the lavages if the patient wishes to do so. More severe reactions require rapid sedation of the patient if necessary with intravenous barbiturates; if the lavages are to be continued, they will have to be done without anesthesia unless the patient has plainly been given an overdose.

(2) *Immediate reaction due to the procedure:* This occurs during and after the lavage and is characterized by dyspnea. It is apparently not due to the pontocaine as it occurs sometimes when very little anesthetic has been used and may not occur at all in the same patient when comparatively large amounts of anesthetic have been given. It is more probably due to reflex spasm of the bronchioles similar to that occurring in bronchial asthma. The symptoms are the same as those of bronchial asthma and may be disquieting to the patient. They must be distinguished from those of the hyperventilation syndrome, which may easily arise from the nervousness of the patient. The symptoms pass off quite rapidly and at the end of an hour have usually completely disappeared and the patient feels himself once again. If this reaction develops during the procedure, treatment should be interrupted and deferred to another day even if the patient wishes to go on.

(3) *Delayed febrile reaction:* This may appear some four to eight hours after the procedure and is probably due to the scattering of bacteria-containing secretions throughout the lung and their subsequent absorption. The mildest reactions of this type consist merely of the general malaise and backache associated with a head cold. There may, however, be a chill and fever up to 100° F. or 101° F. followed by a drenching sweat. Under these circumstances the patient should, of course, go to bed and in the morning will usually feel quite well again. These reactions are not serious or harmful although they may be disturbing to the patient.

(4) *Pleurisy:* Episodes of transient pleuritic pains have been encountered. These consist of sharp inspiratory pains which last a day or two and then subside. Hyperesthesia of the skin of the affected side is usually encountered with these pains.

CONTRAINDICATIONS

According to Stitt this procedure is contraindicated in patients with bronchial asthma, emphysema and heart disease. However, we have treated patients with these conditions without any untoward results. The only serious contraindication is lack of interest or ability to coöperate on the part of the patient. The procedure should not be used on patients who have recently had acute respiratory infections or pulmonary hemorrhages.

FREQUENCY OF TREATMENTS

At first the treatments should be given three to five times a week or more often, as tolerated by the patient. As the procedure becomes simpler and easier for the patient, he is willing to have it more often. For the first two weeks or more it should be done entirely by the physician. Later, the patient should do it under the supervision of the physician and finally he may be permitted to carry on himself at home and report for observation only. When this is possible he should do the procedure daily at first. Later, according to circumstances, the treatments will be gradually spaced at longer intervals.

The time of day selected for the procedure may be a matter of choice with the patient. If it is done at night before going to bed, there is perhaps a better opportunity for bronchial drainage to continue when the patient is lying down. Between the lavage and lying down, however, it is good practice for the patient to breathe deeply twenty to thirty times in order to clear his lungs as completely as possible of any minute plugs of mucus.

This treatment is recommended for all cases of bronchiectasis. It provides the best possible preparation for lobectomy and is far superior to penicillin inhalations alone. For patients unsuitable for surgical treatment or refusing operation it also seems to provide a great amount of relief. We should like to see it applied more extensively in earlier cases and especially in children, in whom the reparative processes are particularly effective. However, children are naturally more nervous about such a procedure than are most adults. Unfortunately,

also, the earlier cases are naturally the ones considered most suitable for surgical treatment. The procedure is also applicable to cases of pulmonary abscess and Stitt has used it effectively in chronic purulent bronchitis.

REPORT OF CASES

The following cases are presented to illustrate the use of this treatment in bronchiectasis. It is not intended to suggest that the studies of the patients have been extensive. Only one has been followed for more than a few months. No studies of bacterial sensitivity were done and no lipiodol bronchograms were made after treatment. However, it was felt that the symptomatic improvement noted in these patients justifies a preliminary report of the technique with notes on these cases to illustrate its use. Further investigation of this treatment has been interrupted by external circumstances, but it is hoped to publish more detailed and more prolonged analyses of a larger group of patients later.

Case 1: A 28-year-old physician was left with a chronic cough after an attack of acute bronchitis at the age of one year. Throughout childhood there were numerous acute respiratory insults, each one of which apparently left him a little worse than before. Since the age of 14 years, and perhaps earlier, there was considerable daily expectoration of purulent sputum. At the age of 16 he had an episode of pneumonia. Thereafter, his general health was very poor, his weight was low and he was subject to frequent attacks of acute respiratory infection which appeared against the background of the chronic productive cough. At the age of 23 a bronchogram showed bilateral lower lobar bronchiectasis. An associated severe pansinusitis was treated at this time without influencing the bronchiectasis. When the patient was 25 years old, he was bringing up at least an ounce of sputum daily. Postural drainage provided the only relief and not much of that. At this time a course of bronchial lavage treatments three times a week was begun according to the Stitt method; a sulfathiazole solution which was retained for an hour after being instilled was used. Improvement was rapid; there was a corresponding increase in general vitality and a gain of about 20 lbs. in weight. The patient became almost completely free of sputum and had little cough. After eight months these treatments were discontinued and some relapse occurred. During the following winter, at the age of 26, two further episodes of pneumonia occurred; despite these setbacks postural drainage held the daily sputum to about 15 cc. A year later the patient began daily self-administered bronchial lavages according to the method described here and on this occasion used penicillin. Improvement was once again rapid and even more gratifying than before. Postural drainage soon became unnecessary, and the patient's sputum became reduced to the expectoration of a tiny amount of mucoid material. The patient has now enjoyed this improvement for over eighteen months during which time treatments have been taken daily with few exceptions. He has gained considerable weight and has increased once more in strength and general vitality. He is now able to carry on a full day of strenuous activity and participate in vigorous tennis matches.

Case 2: A 42-year-old man had a chronic cough from the age of 10 years until the time he was seen by us. At the age of 14 he had had a pulmonary abscess which had apparently healed but which had left him with a severe nonproductive cough. From the age of 29 the cough seemed to become worse and the patient had frequent attacks of respiratory infection. At the age of 34 he had a severe attack of pleurisy which drove him to bed and

eventually out to Arizona, where he remained for several months. Three years later he incurred another bout of upper respiratory infection which developed into pneumonia and left him with a residual chronic productive cough. He continued to expectorate large amounts of sputum and at the time he was first seen by us he was raising about a cupful of sputum daily. The sputum was occasionally slightly foul. In addition, he had bronchial asthma and easily became dyspneic; he had had a few minor episodes of bronchial bleeding. Bronchograms taken at the time of his admission showed extensive bronchiectasis involving both lower lobes, the right middle lobe and the left lingula. He was considered unsuitable for surgical treatment and, as he had obtained no relief from sulfonamide or penicillin therapy, a course of bronchial lavages was recommended. Treatments were given about four or five times a week. The treatments at first tended to make the patient temporarily short of breath, but this became less troublesome as the treatments were continued and the patient's enthusiasm increased as improvement was obtained. The daily sputum was reduced from about a cupful to between 20 and 30 cc. within three weeks and the patient was discharged to continue treatments by himself. It has not been possible to follow this patient here for more than three months, as he left for Arizona, where he was continuing treatments and maintaining improvement when he last reported. He is not in any sense cured, but he has been very gratified at the great reduction in the amount of sputum. Perhaps even more important than this is the reduction in the patient's incessant cough, which has enabled him to sleep much more peacefully, and in fact uninterruptedly for the first time in years. Further improvement is anticipated.

Case 3: A 61-year-old man had been left with a chronic productive cough following an acute respiratory infection at the age of 51. He expectorated about a cupful of sputum daily. For the past three or four years he had also been subject to exertional dyspnea and at times some orthopnea.

Examination showed a poorly nourished man with pronounced pulmonary emphysema and basal râles. Bronchograms revealed bilateral bronchiectasis involving both lower lobes, the right middle lobe and the left lingula. There was electrocardiographic evidence of definite disease of the coronary arteries and his history, together with the electrocardiogram, suggested that he had had a myocardial infarction sometime before his admission.

Bronchial lavage seemed to be the only treatment which promised relief in this case and it was, therefore, started cautiously. The patient was so anxious for relief that he cooperated enthusiastically and soon insisted on taking the treatment without anesthesia. Treatments were given about four or five times a week. The amount of sputum rapidly diminished and at the time he was discharged he was bringing up only about 15 cc. daily. He had also improved considerably in well-being. The patient returned about two months later, having in the meantime ceased treatments following an acute illness the nature of which was not determined although unrelated to the treatments. He had suffered some relapse of symptoms and was advised to resume treatments again at home. He was followed, in all, about three months.

SUMMARY

A simplified technique for therapeutic bronchial lavage is described and recommended for bronchiectasis. This technique together with the direct instillation of penicillin solutions into the trachea offers a very satisfactory medical treat-

ment for the condition and one which can be carried out by the patient himself after suitable instruction. Three case reports are presented to illustrate results.

SUMARIO

El Lavado Bronquial en la Bronquiectasia

Descríbese y recomiéndase una técnica simplificada para el lavado bronquial en el tratamiento de la bronquiectasia. Esta técnica, unida a la instilación intratraqueal directa de soluciones de penicilina, ofrece un tratamiento médico muy satisfactorio para dicho estado, y que puede aplicarse el enfermo mismo después de adiestrarse debidamente. Preséntanse tres historias clínicas para ilustrar el resultado.

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BRONCHIAL ASTHMA IN PULMONARY TUBERCULOSIS¹

AARON A. COHEN

The coincidence of bronchial asthma and active pulmonary tuberculosis is still a subject of speculation. Divergent statements are to be found in the literature, varying from the opinion that tuberculosis of the lungs and asthma are mutually exclusive to the statement that they are mutually dependent. In a recently published book, Urbach and Gottlieb (1) summarize the literature and present the varying views of the older European clinicians who considered the two diseases as being rarely associated or even as excluding each other, and of American observers who have shown that asthma occurs as frequently among tuberculosis patients as in the general population. They also point out that other authors believe tuberculosis predisposes to asthma. In Urbach's own experience (2), 5.5 per cent of 452 asthmatics have their asthma due to a combination of tuberculin hypersensitivity and anatomical changes in the thorax produced by tuberculosis. Feinberg (3) says that active tuberculosis occurs less frequently among asthmatics than in the general population. Tuft (4) states that asthma and tuberculosis are not as infrequently associated as has been reported, and that their coexistence is a matter of coincidence rather than due to specific sensitivity. Unger (5) reports that the association varies with the observer, but is generally low.

The largest series of asthmatics with tuberculosis have been reported by Bray (6), Wiseman and Marty (7), Fraenkel (8), Kupper (9), Harkavy and Hehald (10), Lewison and Freilich (11), Schröder (12), Lichtenstein (13) and Tocker and Davidson (14). Bray found that less than 1 per cent of asthmatics have active pulmonary tuberculosis, and 0.5 per cent of patients with active pulmonary tuberculosis have asthma. Wiseman and Marty report that, of 3,712 discharges from a New York tuberculosis sanatorium, 0.6 per cent had asthma. Kupper is quoted as saying that, in 1,000 tuberculosis patients, 1.4 per cent had true asthma. Fraenkel found that 4.3 per cent of 369 asthmatics had active tuberculosis. Harkavy and Hehald found 10 per cent of 400 asthmatics with pulmonary tuberculosis, but only 4.5 per cent were stated to have active tuberculosis. Lewison and Freilich found 51 cases of asthma with active pulmonary tuberculosis in the records of three Chicago hospitals but do not state the percentages. Schröder is quoted as reporting 0.6 per cent patients with asthma in 8,971 tuberculosis patients. Lichtenstein found 1 per cent of asthmatics in 1,000 tuberculosis patients. The best recent report is that of Tocker and Davidson from Sea View Hospital. They studied 386 adult patients with pulmonary tuberculosis by means of careful allergy histories, personal observation, and skin testing among those with personal or family history of allergic disease. They found 3.1 per cent with bronchial asthma, a total of 12 patients. While small, this series has the advantage of being personally observed by the authors reporting them. The significance of this will be appreciated later. However, they apparently did not bronchoscope all their patients.

¹ From the Olive View Sanatorium, Olive View, California.

To summarize the published statistics, we find that the reported occurrence of asthma in pulmonary tuberculosis varies from 0.5 (Bray) to 3.1 per cent (Tocker and Davidson), and the frequency of active pulmonary tuberculosis among asthmatics varies from 1 (Bray) to 4.5 per cent (Harkavy and Hebdal). For comparison, the prevalence of asthma in the general population is 1 to 2 per cent according to Tuft, or between 3.1 to 3.6 per cent according to Tocker and Davidson. The prevalence of active pulmonary tuberculosis in the general population is estimated to be about 0.5 per cent, according to Bogen (15). In brief, the reported prevalence of asthma among selected groups of tuberculosis patients is in the same range of figures as in the general population, while the reported prevalence of active tuberculosis in three selected groups of asthmatics is higher than in the general population. We must emphasize that these figures on the association of the two diseases are from selected small groups and probably bear no close resemblance to the actual coincidence of tuberculosis and asthma.

PRESENT STUDY

In an effort to shed light on some of the interesting features in the association of asthma and tuberculosis, all the charts of patients discharged with the diagnosis of bronchial asthma from Olive View Sanatorium in the period from July 1, 1936 to July 1, 1946 have been reviewed. In addition, 9 patients currently being observed at the Sanatorium were studied.

As the basis for selection, the diagnosis of pulmonary tuberculosis had to be substantiated by a positive sputum or by suitable clinical and X-ray considerations.

The selection of the true asthmatics was a difficult task. Tocker and Davidson had the advantage of personally observing their reported cases. In a study based on records of patients no longer in the institution, it is striking how vague the diagnosis of bronchial asthma often seems to have been. It is common knowledge that all that wheezes is not asthma, especially among tuberculosis patients. Just as a heart murmur is produced by blood flowing past a point of relative obstruction, so a wheeze may be caused by air flowing past a point of relative or absolute bronchial narrowing, which may be due to:

- (1) Thick sputum, foreign body, intrabronchial tumor.
- (2) Inflammatory changes in the bronchial wall due to tuberculous or other bronchitis.
- (3) Kinking of a bronchus due to collapse treatment or fibrosis.
- (4) External pressure from an enlarged lymph node or tumor.
- (5) Bronchospasm due to histamine or to vagal stimuli from an irritating focus (16), or from cardiac failure (28).
- (6) Emphysema, with a thorax overfilled with air, compressing the bronchioles.

In an effort to be as precise as possible in our review, we defined asthma as recurrent paroxysmal dyspnea, with bilateral wheezing, in patients with or without other associated allergic manifestations, with or without a family history of allergy. The attacks can be traced to specific sensitizing agents usually by testing or clinical experience, and the symptoms can be alleviated by avoidance

of or desensitization to these allergens. The attacks usually respond favorably to treatment with broncho-dilating drugs. Bronchoscopy should be done to rule out nonspecific factors.

Needless to say, all these criteria were rarely satisfied in the series reviewed. Cases were found in which asthmatic attacks were described prior to Sanatorium entry, but without subsequent attacks in the Sanatorium. These were not included unless the stories were typical. Others had asthmatic attacks in the Sanatorium without bronchoscopic examination or with bronchoscopically proved tuberculous endobronchitis. These attacks were not called definite asthma, unless typical and antedating the onset of tuberculosis, or, unless they followed the onset of tuberculosis with negative bronchoscopic findings were called definitely asthmatic if they otherwise fitted the description given above.

There might be some debate about hesitating to call definite asthma those attacks occurring after the onset of tuberculosis in patients not bronchoscoped or in those with tuberculous endobronchitis. One might claim that typical paroxysmal bilateral wheezing in a patient with a unilateral endobronchial tuberculous lesion may be due to diffuse bronchospasm produced by local irritation in a person predisposed by heredity to asthma, just as nonspecific factors, such as emotion or smoke, may produce typical asthmatic attacks. I wonder also if diffuse bronchospasm brought on by a local irritant focus could not occur in a person with vagal irritability who had no asthmatic tendency.

At any rate, using the criteria above described, our findings are as follows:

Frequency of Asthma and Tuberculosis

Total patients discharged, 7/1/36-7/1/46.....	7,301			
Males.....	3,564			
Females.....	3,660			
Caucasian, approximately 50%.....				
Mexican, approximately 33%.....				
Negro and Oriental 17%.....				
Total patients discharged 7/1/36-7/1/46 with chart diagnosis "bronchial asthma".....	58 or 0.8%			
Nontuberculous patients.....	3			
Patients with tuberculosis and "asthma".....	55	0.75%		
Definite asthma* and tuberculosis.....	36	0.5%		
Questionable asthma and tuberculosis.....	19	0.25%		
Of the definite asthmatics* with tuberculosis.....				
Males.....	25			21
Females.....	6			15
Caucasian.....				
Mexican.....				
Negro.....		3		
Japanese.....		1		
Filipino.....			1	
Age Distribution of 36 Patients with Tuberculosis and Asthma*				
0-10 years.....	1			
11-20.....	5			
21-30.....	6			
31-40.....		20		
41-50.....			2	
51-.....				2

* According to the criteria mentioned above.

It is thus seen that in our series the prevalence of asthma and pulmonary tuberculosis, counting only those who seemed to have definite asthma, is 0.5 per cent. This compares with the prevalence of asthma in the general population of 1 to 2 per cent, as stated by Tuft (4), or 3.1 to 3.6 per cent, as stated by Tocker and Davidson (14). Our figure of 0.5 per cent compares with the 0.5 per cent prevalence of asthma in tuberculous patients given by Bray (6), with the 0.6 per cent given by Wiseman and Marty (7), with the 1.4 per cent given by Kupper (9), and with the 3.1 per cent given by Tocker and Davidson (14).

Precedence of Tuberculosis or Asthma

Among our group of 36 patients who seemed to have definite bronchial asthma, the onset of asthma preceded that of tuberculosis in 34, and the onset of tuberculosis preceded that of asthma in 2. Among the 12 cases of Tocker and Davidson, 7 had asthma preceding tuberculosis, 2 had tuberculosis preceding asthma, and in the remaining 3 no precedence could be stated. It is apparent that tuberculosis does not often precipitate asthma in previously nonasthmatic persons.

Atopic Features

In our group, 3 patients had a diagnosis of hay fever with asthma. The family histories of allergic tendencies were not considered reliable; therefore, no figures are quoted. Of Tocker and Davidson's 12 asthmatics, 6 had a family history of atopy. They were in a position to determine the frequency of hay fever in their series of tuberculosis patients, which was 2.8 per cent, or almost as many as had asthma. Only 2, however, had both hay fever and asthma. From their data they conclude that tuberculosis does not precipitate asthma, since they regard hay fever as a precursor of asthma. They found, in addition, 14 patients who had a family history of allergy but who themselves were asymptomatic. This again bolstered their belief that tuberculosis does not predispose to asthma.

Twenty-two of our patients had skin tests with allergens either before or during hospitalization at Olive View. Because the testing technique at Olive View was not standardized and not in the hands of one person, the results cannot be accepted without qualification, and no further attempt at analysis of this aspect will be made. Tocker and Davidson, using a standardized technique of intracutaneous testing, found that the offending antigens were the same as in the general population, but that the positive skin tests were generally weaker than in nontuberculous patients. They do not give the results of desensitization treatment, nor are our data reliable on this point.

Type of Tuberculosis

In our 36 patients, 16 had predominantly exudative lesions, 14 had exudative-productive lesions and 3 had predominantly productive or fibroid lesions. As for extent of the involvement, 3 were diagnosed as primary, none as minimal, 8 as moderately advanced and 24 as far advanced. One had only a tuberculous empyema. Almost all the cases listed in their charts by Tocker and Davidson were of the caseo-pneumonic type, with fibroid cases in the great minority. This

is of interest because it has been stated that the type of tuberculosis associated with asthma is fibroid (17), and also because Urbach and Locw (2) have described so-called tuberculo-allergic asthma in association with the chronic fibroid type of pulmonary tuberculosis. It must be recognized, however, that at Olive View we do not have many patients of the chronic fibrotic domiciliary type.

Severity of Asthma

The severity of asthma in our patients is presented in table 1. This shows that most of the moderate and severe asthma occurred in patients with far advanced tuberculosis and in the exudative and exudative-productive types, and that the majority of the far advanced patients with asthma had moderate to severe degrees of asthma.

TABLE 1
Severity of asthma according to extent and type of tuberculosis

SEVERITY OF ASTHMA	MODERATELY ADVANCED	FAR ADVANCED	EXUDATIVE	EXUDATIVE-PRODUCTIVE	PRODUCTIVE
0*					
1	2	3	2	3	2
2	2	4	5	0	
3	2	9	4	6	1
	2	8	4	5	

* 0 indicates no attacks at Olive View; 1 indicates mild attacks; 2 indicates moderate attacks; 3 means severe attacks.

Mutual Effects of Tuberculosis and Asthma

The most interesting question of all was what effect, if any, asthma had on tuberculosis, and *vice versa*. In none of our patients could it be definitely established that tuberculosis aggravated or ameliorated asthma, although it was stated in a few charts that asthma which had been present before entry to the Sanatorium did not occur at Olive View. Our asthma histories were not complete enough to give all the data desired on this point. Tocker and Davidson found that, in most of their cases in which asthma preceded tuberculosis, the asthma was improved with the onset of tuberculosis, and that it became worse with the healing of tuberculosis. This effect has been noted in other intercurrent infections (5). It might also be due to environmental factors in the hospital and to antiasthmatic treatment given in the hospital. They are not specific on these points.

In 34 of our group of 36 asthmatics, no effect of asthma on tuberculosis could be determined, although in 9 patients the asthma was severe. Of the 9 with severe asthma, 3 left the hospital with their tuberculous status unimproved, 2 left as improved, one left as quiescent and 3 left as apparently arrested. In 2 patients it seemed possible that the asthma had a deleterious effect on the tuberculosis. Both of these had severe asthma, with enlargement of cavities

after prolonged asthmatic bouts; both had complicating endobronchial tuberculosis.

One would expect that severe asthma, with its associated cough, increased secretions and violent respiratory efforts, would more frequently affect adversely associated pulmonary tuberculosis. The 34 patients with coexistent asthma and tuberculosis who did not seem to be affected adversely by their asthma did not all do well, but they appeared to have adequate explanation for this by reason of their tuberculous condition alone. None of our patients had any obvious relation between asthmatic attacks and hemoptysis. None of our pneumothorax patients had any complication due to asthma.

In connection with the harmful effect of asthma on associated tuberculosis, Tocker and Davidson had no patients showing such results. Urbach and Gottlieb (1) quote Vaccarezza and Acevedo (18) to the effect that asthma may complicate pneumothorax treatment by causing temporary reëxpansion of the lungs, or by blowing up cavities. Unger (5) quotes Wilson (19) and Gordon (20) to the effect that asthma reactivates latent tuberculous lesions, and that untreated allergy makes the prognosis of tuberculosis worse. Wiseman and Marty (7) report a possible case of an acute dissemination of pulmonary tuberculosis during *status asthmaticus*. They quote Hajos (21) as saying that asthma usually does not activate tuberculosis. Other references on this point are given by Tocker and Davidson (14). Few clear-cut instances of harmful effects of asthma on tuberculosis have been published.

Endobronchial Tuberculosis and Asthma

Another point of much interest is the association of bronchial asthma and tuberculous endobronchitis. Our experience is as follows:

Number of tuberculosis patients with definite asthma	
bronchoscoped.....	18
Number with negative findings.....	10
Number with positive findings.....	8
Number of tuberculosis patients with severe asthma	
bronchoscoped.....	6
Number with negative findings.....	1
Number with positive findings.....	5

Of the 8 patients with positive bronchoscopic findings, 3 had asthma that was mild to moderate, and these had only minimal endobronchial lesions. Five remaining patients with positive bronchoscopic findings were severe asthmatics, and these had ulcero-stenotic endobronchitis.

To put it another way, there were 11 severe asthmatics in all; one of these had negative bronchoscopic findings; 5 had ulcero-stenotic lesions; 5 with severe asthma were, unfortunately, not bronchoscoped.

Tuberculous tracheobronchitis has been variously estimated to occur in 11 to 40 per cent of patients with pulmonary tuberculosis, depending on whether the studies were done routinely on all admissions or at autopsy (23, 24, 25, 26). The

frequency at Olive View, reported by Hawkins (27), was 25 per cent. From the incomplete data available in our asthmatics, it would seem that severe asthma was often associated with serious endobronchial complications. Oatway *et al.* (22) have been the only previous observers of whom we are aware who have commented on the association of endobronchial tuberculosis and allergic disease. They studied 50 patients with endobronchial tuberculosis and found that 45 per cent of the females and 30 per cent of the males had histories of allergic

TABLE 2

Positive bronchoscopic findings correlated with severity of asthma

PATIENT	SEX	FINDINGS ON BRONCHOSCOPY	SEVERITY OF ASTHMA
D. S.	m	RUL edema and small ulcers	Severe
F. B.	f	RUL stenosis	Severe
C. C.	f	LMB stenosis	Severe
G. F.	f	RUL stenosis and granulations	Severe
A. S.	m	RUL stenosis, RMB submucous nodules	Severe
P. C.	f	LMB slight external compression	Mild
J. M.	m	RUL and RMB submucous nodules	Moderate
R. M.	m	1942-LMB submucous nodules 1944-negative	Moderate

RUL = right upper lobe orifice.

RMB = right main bronchus.

LMB = left main bronchus.

It is of interest that we had one patient with stenosis and granulations involving the right upper lobe orifice, who developed asthma after she contracted tuberculosis. She had a family history of asthma. She was found sensitive to a number of pollens. One wonders whether this was an instance of pulmonary and endobronchial tuberculosis precipitating overt asthma in a person constitutionally predisposed to it.

Current Cases

In addition to the 36 patients discussed above, we have had 8 hospitalized patients and one non-hospitalized patient with tuberculosis and asthma under observation since July, 1946. They are 8 adults and one child, 5 females and 4 males. Seven have had far advanced pulmonary tuberculosis and 2 moderately advanced lesions. In 4 tuberculosis clearly antedated the onset of asthma, and in 4 asthma preceded tuberculosis. In 4 asthma has been of severe degree, and Eight of the 9 patients have been bronchoscoped, some repeatedly. Major bronchoscopic findings of tuberculous endobronchitis have been found in 3 patients. In 2 of these 3, asthma has been severe and in one not prominent; repeated bronchoscopy in this last patient has recently shown only diffuse reddening of the right main bronchus. In the 2 additional severe asthmatics no endobronchial lesions were found. In no patient has the complicating asthma unquestionably been a factor upsetting the status of tuberculosis and causing undesirable tuberculous complications, although there is in each a possibility that such may have been the case. A brief outline of each case will reveal the salient points.

CASE REPORTS

A.McK., aged 40, a white male, had far advanced pulmonary tuberculosis with bilateral scattered fibro-exudative infiltrations, which cleared partially during his Sanatorium stay. Bronchoscopic findings at Olive View were normal. He had had asthma for eighteen years preceding the development of tuberculosis, with undoubted bronchiectasis. The asthma was severe at Olive View. There was no allergic rhinitis. He had a family history of asthma. The patient was found sensitive to house dust and showed gratifying improvement from house dust desensitization and penicillin aerosol. His asthma did not prevent regression of his tuberculosis.

A.H., aged 36, a white female, had far advanced pulmonary tuberculosis. The lesions were exudative with multiple cavities, and she had a left pneumothorax. The onset of tuberculosis was in 1937. Bronchoscopy showed normal findings. She left the Sanatorium with her tuberculosis improved, but against medical advice. The onset of her asthma was in 1945. At Olive View she had moderate to severe attacks of asthma with allergic rhinitis. The family history was negative for allergy. She was found sensitive to house dust, with good results from desensitization. There was no obvious relation between the course of her asthma and the course of her tuberculosis.

M.R., aged 41, a white female, had far advanced productive and caseo-ulcerative lesions in the lungs and she had a right thoracoplasty. The onset of her tuberculosis was in 1940.

There has been a gradual deterioration of her condition. Bronchoscopy showed a progressive ulcero-stenotic lesion of the right main bronchus extending into the lower trachea. She has had hay fever and asthma since 1918. Her asthma was mild from 1930 to 1943 and since then severe. Her family history was negative for allergy. She was found sensitive to house dust and several pollens. An inadequate trial of desensitization treatment gave poor results. In this case it is difficult to tell how much of the wheezing, dyspnea and cough are due to endobronchial tuberculosis and how much to asthma. She wheezes in both lungs and gets little relief from adrenalin or aminophyllin. Her symptoms are probably largely due to tracheobronchial tuberculousis.

I.S., aged 24, a white female, has far advanced pulmonary tuberculosis, productive in type, with a left pneumothorax. Tuberculosis was discovered in 1939. Her condition has been quiescent. Bronchoscopy revealed no lesions. The onset of her asthma was in 1936. There has been occasional mild asthma at Olive View, but severe attacks on her visits home (attributed to a pet dog). She is sensitive to house dust, pollens and danders. Allergic rhinitis is troublesome at Olive View, with not entirely satisfactory results from desensitization. The patient has incomplete collapse of the left lung due to adhesions, and has had occasional positive sputum cultures, also a small persisting left pleural effusion. She developed severe asthma following her last Christmas visit at home and returned with increased pleural effusion and a positive sputum culture. Her pneumothorax has probably never been completely effective. The aggravating effect of her asthma is difficult to evaluate. Recent bronchoscopy has revealed no lesion.

J.F., aged 27, a white male, has far advanced pulmonary tuberculosis, productive in character, with bilateral thoracoplasty, pneumoperitoneum and a persisting cavity. The onset of tuberculosis was in 1937. Bronchoscopy has recently not revealed any abnormality. Onset of asthma of moderate severity was in July, 1946. Recently he developed a cavity at the site of a previously present round caseous focus. The asthma has responded well to desensitization with house dust and grass pollen. Allergic rhinitis is mild. The family history is negative for allergy. The moderately severe asthma probably did not contribute to the breakdown of the round caseous focus.

J. L., aged 30, a white male, has far advanced pulmonary tuberculosis, exudative in type, with a cavity and an ineffective right pneumothorax. The onset of tuberculosis was in 1945. Bronchoscopy on admission showed edema and occlusion of the dorsal branch orifice of the right lower lobe; recent bronchoscopy showed diffuse erythema of the right bronchial tree without occlusion. The onset of asthma was in early childhood. The family history is negative for allergy. Allergic rhinitis was previously present. His asthma ceased about the time tuberculosis began. The patient is sensitive by test to house dust. No desensitization treatment is necessary at this time. The improvement of his asthma with the onset of tuberculosis is of interest; similar observations have been mentioned by Tocker and Davidson (14).

R.T., aged 38, white female, has far advanced pulmonary tuberculosis, with an atelectatic left upper lobe containing a cavity. The onset of tuberculosis was in 1933. A left pneumothorax was started in 1936 for an upper lobe cavity. She was discharged as quiescent in 1938, with the cavity apparently closed. Bronchoscopy had not been done. The pneumothorax space was lost in 1939. Asthma began in 1938 and occurred each year during winter and was moderate to severe in degree. In June, 1946 there was a

flare-up of the tuberculosis. She was readmitted with an atelectatic left upper lobe containing a cavity. Bronchoscopy now revealed an extensive ulcero-stenotic lesion of the left main bronchus, for which streptomycin treatment was recently begun. At Olive View her asthma was severe with bilateral wheezing. There was occasional mild allergic rhinitis. She was found to be sensitive to house dust, and there has been very good response to desensitization, even before streptomycin therapy was started. A daughter has asthma. This case illustrates the difficulties in the differential diagnosis of asthmatoïd symptoms. This patient's wheezing, cough and paroxysmal dyspnea are probably due to asthma, in view of the bilateral nature of the wheeze, the allergic family history, the known sensitivity to house dust and her favorable response to desensitization treatment. But she also has tuberculous ulceration with stenosis of the left main bronchus. The effect of the asthma on the endobronchial lesion is an interesting subject for speculation.

C.S., a Negro boy, 5 years old, has moderately advanced pulmonary tuberculosis with an exudative lesion in the right base and left hilar enlargement. The condition was stationary until very recently, when progression of the pulmonary lesion in the right lower lung-field occurred. He has been bronchoscoped with negative findings. The onset of his tuberculosis was in 1944. Wheezing and a chronic rhinitis have been noted since 1944. At Olive View the wheezing has been perennial, moderate and bilateral, and he has had a persistent blood eosinophilia up to 16 per cent. He had eczema at 6 months of age. His grandmother died of asthma. The boy is sensitive to pollens and house dust, and desensitization treatment was begun recently.

E.H., aged 36, a white female, had moderately advanced pulmonary tuberculosis, productive in type, with no change in the fibro-calcific lesion since 1941. The onset of tuberculosis was in 1938. Bronchoscopy, performed in 1944 because of premenstrual hemoptyses, showed moderate stenosis of the right main bronchus. She had very occasional positive gastric cultures during episodes of upper respiratory infections and at her puerperium. The onset of asthma was in the spring of 1946. She was found sensitive to house dust and desensitization was started. She had a family history of allergy. Her asthma became worse in December, 1946, probably due to overtreatment with house dust antigen. Soon after this she had an upper respiratory infection and an isolated sputum concentrate positive for tubercle bacilli. Repeated bronchoscopy in January, 1947 showed no lesion. The upper respiratory infection subsided, the asthma again responded well to treatment, and no further positive sputa were found. In this patient there is a possible relation between her asthma, the upper respiratory infection and the isolated positive sputum.

SUMMARY AND CONCLUSIONS

1. In a ten-year period from 1936 to 1946, 55 patients out of 7,301 discharged from Olive View Sanatorium were diagnosed as pulmonary tuberculosis and bronchial asthma, an incidence of 0.75 per cent.
2. Of these, 36 seem to have an adequate basis for the diagnosis of asthma, an incidence of 0.5 per cent. We have 9 additional patients with asthma and tuberculosis under current observation.
3. In our series of tuberculous patients asthma occurred less frequently than in the general population.

4. In 34 discharged and 4 current patients, asthma preceded tuberculosis and, in 2 discharged and 4 current patients, tuberculosis preceded asthma.
5. There is no evidence in our group that tuberculosis predisposes to asthma, although it may have done so in the 6 patients in whom it preceded the asthma, nor that asthma predisposes to tuberculosis.
6. We could not substantiate the claim that asthma is associated with the fibroid type of tuberculosis.
7. In 34 of our discharged patients and in 9 current patients, asthma had no unquestionably deleterious effect on tuberculosis. No correlation could be made between the severity of asthma and the precedence of tuberculosis.
8. In our group, severe asthma tended to be associated with serious tuberculous endobronchial complications.
9. We have no recognized instance of asthma of the "tuberculo-allergic" type, such as Urbach and Loew report.

SUMARIO Y CONCLUSIONES

El Asma Bronquial en la Tuberculosis Pulmonar

1. En el decenio 1936-1946, hizose el diagnóstico de tuberculosis pulmonar y asma bronquial en 55 enfermos de 7,301 dados de alta del Olive View Sanatorium, o sea una incidencia de 0.75 por ciento.
2. En 36 de ellos (0.5 por ciento) parecía que había una base adecuada para el diagnóstico de asma. Otros 9 enfermos con asma y tuberculosis continúan en observación.
3. En esta serie de tuberculosos el asma se presentó con menos frecuencia que en la población general.
4. En 34 enfermos dados de alta y 4 en observación, el asma precedió a la tuberculosis, en tanto que sucedió lo contrario en 2 dados de alta y 4 en tratamiento.
5. En este grupo no hay pruebas de que la tuberculosis predisponga al asma, si bien puede haber sucedido así en los 6 enfermos en que precedió a la última, ni de que el asma predisponga a la tuberculosis.
6. No pudo comprobarse el aserto de que el asma se asocie con la forma fibrosa de la tuberculosis.
7. En 34 de los dados de alta y en 6 de los enfermos en tratamiento, el asma no ejerció efecto nocivo indiscutible sobre la tuberculosis. No pudo correlacionarse la gravedad del asma con la precedencia de la tuberculosis.
8. En este grupo, el asma grave reveló tendencia a asociarse con serias complicaciones endobronquiales tuberculosas.
9. No se reconoció ningún caso de asma del tipo "tuberculo-alérgico" comunicado por Urbach y Loew.

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PRODUCTION OF PLEURAL ADHESIONS FOR THERAPEUTIC PURPOSES¹

JOHN D. STEELE

The experimental production of pleural adhesions has been fairly extensively reported in the medical literature, although reports of clinical results have been meager. Bethune (1) made the first comprehensive study of this subject and concluded that insufflation of iodized talc, under thoracoscopic guidance, was the most satisfactory method of producing such adhesions. Following subsequent experiments, Singer, Jones and Tragerman (2) concluded that talc in any form produced the most desirable adhesions and that the addition of iodine was not essential. Hanrahan, Adams and Klopstock (3, 4) concluded that the injection of a suspension of talc into the pleural cavity was as effective as insufflation. Gowar (5), on the other hand, found insufflation yielded better results than injection.

We feel that obliteration of the pleural cavity by the production of adhesions is indicated, first, in certain cases of recurrent spontaneous pneumothorax when the recurrences are frequent and disabling and, second, in preparation for extrapleural pneumonolysis in cases of pulmonary tuberculosis when a free pleural space exists beneath the proposed area of dissection to prevent perforation into the pleural cavity at the time of operation.

We have introduced irritants 36 times in attempts to produce pleural adhesions in a total of 24 patients. Six patients with recurrent spontaneous pneumothoraces were so treated. In one of these, the procedure was carried out on both sides. In 18 patients with pulmonary tuberculosis, irritants were introduced preliminary to extrapleural pneumonolysis with paraffin filling in 10 (one bilateral case); preliminary to extrapleural pneumothorax in 5; and preliminary to cavernostomy in 3. (We no longer use this latter indication since our cavernostomies are now performed after preliminary surgical incision and packing of the chest wall.)

Poudrage with iodized talc, according to the method of Bethune, was used for our first patient in 1940 prior to publication of the results of Hanrahan *et al.* of the use of talc suspensions. In the next 11 patients, injection of irritants was employed; then, because of a high percentage of failures, the injection technique was abandoned and poudrage with plain talc was used exclusively in the remaining patients. In addition to the use of talc, either by injection or poudrage, the injection of a saturated solution of glucose was employed in 3 instances.

TECHNIQUE

In our patients in whom talc was introduced by injection into the pleural cavity, a small pneumothorax was first induced with oxygen. The talc suspension was next injected and all available oxygen then withdrawn. Oxygen was used for the pneumothorax instead of air because it was believed that any residual gas, not withdrawn, would be ab-

¹ From the Department of Surgery, Muirdale Sanatorium, Milwaukee 13, Wisconsin.

sorbed more rapidly than air. In most instances, 2 g. of talc suspended in 10 cc. of distilled water was employed. Following the procedure, the patient was moved about frequently in bed in order to facilitate distribution of the talc in the pleural cavity.

In our cases in which talc was introduced by poudrage, a series of pneumothorax refills was given with air until the pneumothorax was considered large enough to allow manipulation of the thoracoscope. A single thoracoscopic cannula was then introduced and the powder insufflated into the pleural cavity by means of a powder atomizer to which a catheter was attached. Insufflation was continued until both pleural surfaces were evenly covered with talc, as observed through the thoracoscope. All available air was withdrawn at the conclusion of the procedure. In our cases of recurrent spontaneous pneumothorax, the lung was allowed to reexpand, indicating closure of the bronchopleural fistula, and pneumothorax reintroduced artificially before the poudrage was performed. In our earlier cases approximately 3 g. of talc was insufflated at the time of poudrage; in our later cases 8 to 10 g. of powder has been used with uniformly satisfactory results.

In 2 cases, the pneumothorax space was too small to allow introduction of the thoracoscope. In these cases, the powder insufflations were carried out through a large bore needle.

REACTIONS

All patients had some degree of pain following either injection or insufflation of talc into their pleural cavities. A few complained bitterly as soon as the talc came in contact with their pleural surfaces; the majority complained for the first time when the visceral and parietal pleural surfaces were brought into apposition on withdrawal of the gas from the pleural cavity at the conclusion of the procedure. In all patients, the pain was most severe during the first twenty-four hours but sometimes persisted for three to five days. Ten patients, having a total of 18 injections of talc suspensions, required an average of 4.2 doses of narcotics following the procedure; 14 patients having a total of 16 poudrages required an average of 6.0 doses.

Nearly all of our patients had fever which reached a peak in twenty-four to forty-eight hours. The average of these peaks in the patients receiving talc injections was 100.2°F. ; in those having poudrages, 101.2°F. In general, the fever was of slightly longer duration in those having poudrages. In the majority, the temperature was normal within one week of the procedure, although fever of low grade persisted in a few patients up to ten days or two weeks.

The irritation of the pleura by the talc might reasonably be expected to cause the production of effusions. However, in only about half of our cases was enough fluid present to be recognized on radiographic or fluoroscopic examination. Thoracentesis was performed in only 3 patients, all of whom had had poudrages. The largest amount of fluid aspirated from a single patient was 590 cc. (total for 3 aspirations).

There was no apparent correlation between the severity of symptoms following the introduction of talc into the pleural cavity and the success of the procedure. In many cases, mild to marked pleural reactions were apparent on roentgenograms taken within a few days after the procedure. Such reactions subside

within a week or two, although it is not uncommon to note some pleural thickening, particularly in the interlobar fissures, for months or even years afterward. On clinical examination no patient had an appreciable loss of pulmonary expansion or pulmonary function, but no tests were performed to measure respiratory reserve. In a few cases, densities evidently due to collections of the talc on the pleural surfaces were seen on the roentgenogram for several months following a poudrage.

RESULTS

The results of our attempts to produce pleural adhesions are based on our observations at operation, on our ability or inability to reinduce pneumothorax or in certain cases of recurrent spontaneous pneumothorax, on a period of observation during which the patients were observed for evidence of recurrence. The final results in 13 patients were evaluated at operation and in 4 following attempts to reinduce pneumothorax. In 5 patients, who had had frequently recurring spontaneous pneumothoraces, 4 have had no recurrence for periods of from one and one-half to six years; in the fifth, a partial pneumothorax recurred about two years following poudrage. We believe that this recurrence was due to failure to approximate the pleural surfaces immediately after the poudrage because of a recurrence of the bronchopleural fistula at the time of the operation. The results in 2 of our patients who left the Sanatorium before their contemplated procedures were carried out are unknown.

Of 16 attempts to produce pleural adhesions by the injection of talc suspensions, 5 yielded satisfactory and 11 unsatisfactory results as far as the obliteration of the pleural cavity was concerned. Our 3 attempts to produce adhesions with saturated glucose solutions were all unsatisfactory. Of the patients having injections of talc or glucose, 5 received more than one injection; one of these had a total of 5 unsuccessful attempts to produce obliteration of his pleural cavity. Poudrage produced obliteration of the pleural cavity in 12 instances and failed in 2. One of these failures has already been mentioned. The other occurred early in our series when we were using relatively small amounts of talc. Since using 8 to 10 g. of talc, our results have been uniformly satisfactory. Adhesions following a poudrage become relatively firm in from six to eight weeks.

SUMMARY

Obliteration of the pleural cavity by the production of adhesions was attempted 36 times in 24 patients. Insufflation of talc was found to yield far better results than injection of talc suspensions. Insufflation produced obliteration of the pleural cavity in 12 instances and failed in 2; injection produced obliteration in 5 instances and failed in 14.

Principal indications for the induced obliteration of the pleural space are recurrent spontaneous pneumothoraces and, in patients with pulmonary tuberculosis, preparation for extrapleural pneumonolysis where a free pleural space exists beneath the proposed area of dissection.

SUMARIO

La Producción de Adherencias Pleurales con Fines Terapéuticos

En 24 enfermos se probó 36 veces la obliteración de la cavidad pleural mediante la producción de adherencias. La insuflación de talco dió resultados muchos mejores que la inyección de suspensiones de talco.

Las principales indicaciones para provocar la obliteración del espacio pleural residen en los neumotóraces espontáneos recurrentes y, en los tuberculosos pulmonares, en la preparación para la neumonolisis extrapleural cuando existe un espacio pleural despejado debajo de la propuesta zona de disección.

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HEMORRHAGE FROM INTERCOSTAL VESSEL

A Case Occurring during Thoracoscopy

C. G. BAYLISS¹

The patient was a male, age 24, suffering from bilateral pulmonary tuberculosis. Artificial pneumothorax had been commenced on the right side, at the Queen Victoria Home for patients suffering from pulmonary tuberculosis, Wentworth Falls, New South Wales, two months prior to the incident to be described. At the time of induction of pneumothorax, there was present extensive infiltration throughout the upper two-thirds of the right lung with obvious cavitation, and in the left lung a moderate amount of infiltration in the mid-zone. He had been referred for thoracoscopic examination because of pleural adhesions which were preventing effective relaxation of the lung. The appearance of the skiagram indicated that the adhesions were extensive and probably unsuitable for pneumonolysis. However, it was decided to perform thoracoscopy and defer the decision regarding pneumonolysis until the adhesions had been seen.

The thoracoscopy was the 457th personally carried out and the "two-cannula" technique was employed. The first puncture was made in the mid axillary region in the third intercostal space. When the trocar was withdrawn blood-flecked bubbles appeared at the external orifice of the cannula with each respiration. As I had never previously remarked this, I suspected that a vessel might have been injured and as rapidly as possible made a second puncture. This was made about two inches inferior to the first puncture. With the telescope introduced through the second cannula, blood could be seen spurting vigorously into the pleural cavity from the internal orifice of the first puncture. From the force of the spurts the bleeding was obviously from the intercostal artery or one of its main branches. A third puncture was then made posterior to the angle of the scapula. With the telescope in position through the second cannula the cautery rod was introduced through the cannula in position in the third puncture, and the tip applied just inside the orifice from which the blood was spurting. Because of the quantity of blood through which the tip had to be passed the latter was used rather hotter than usual. By what must be considered a somewhat lucky chance, the tip immediately touched the bleeding spot and with continued application for a few seconds led to coagulation and control of the hemorrhage. After I was satisfied that bleeding had ceased, I removed with the sucker the blood which had been shed into the pleural cavity. This amounted to over two pints. As all speed had been exerted in making the second and third punctures, the quantity of blood lost gives an indication of the size of the vessel which had been injured.

The patient, although rather shocked from the rapid blood loss, quickly recovered after the hemorrhage was controlled.

As a matter of passing interest, after inspection of the adhesions, I would in any case have decided that pneumonolysis should not have been attempted.

COMMENT

Serious bleeding from an intercostal vessel damaged by the trocar seems to be a rare accident in the course of thoracoscopic examinations. Goorwitch (1) notes the occurrence in one of his own patients of hemorrhage, the source of

¹ 147 Macquarie Street, Sydney, N.S.W., Australia.

which he believes to have been an intercostal vein traumatized at operation by the trocar.

Since the operation noted above, I have carried out 44 more thorascopic examinations, making a total of over 500 operations which I performed. This is the only occasion upon which I have experienced bleeding of this type. In one of my earlier cases, steady although not severe bleeding was still taking place from the internal orifice of a puncture at the termination of an operation which had lasted about forty minutes. This bleeding perhaps would have stopped spontaneously but I applied the cautery in the way described above and stopped this bleeding. However, neither in the character of the bleeding nor in the amount of blood lost was this case comparable to the case above described.

Normally, in the position in which the first puncture was made in this case, the intercostal vessels are well protected. Whether in this instance the intercostal vessels were less well protected than usual, whether there was an unusual branch of the artery crossing the intercostal space or whether I was not sufficiently careful in ensuring that the point of the trocar was directed away from the inferior border of the superior rib, I do not know. At any rate the lesson is plain that care should always be taken that the latter is done.

As regards the control of the hemorrhage, there was certainly an element of good fortune in that I was able to control it so easily. If I had not been able to do so by the means employed, it would have been necessary to have removed a piece of rib and located the bleeding point and effected hemostasis in the ordinary way.

SUMMARY

A case of severe hemorrhage caused by injury to an intercostal vessel by the trocar in the course of a thorascopic examination is described.

The incidence of this accident, possible factors associated with its occurrence and the method employed for its control are briefly commented upon.

SUMARIO

Hemorragia de un Vaso Intercostal: Caso Observado durante la Torascopia

El caso descrito es de hemorragia grave ocasionada por lesión de un vaso intercostal por el trócar durante un examen torascópico.

Coméntanse sucintamente la incidencia del percance, los factores posiblemente asociados con el mismo y el método empleado para cohibirlo.

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showed evidence of fluid or thickened pleura over the lower two-thirds on the left side with bronchovesicular breath sounds over the apex; no râles were heard. The right lung was normal. All reflexes were equal and hyperactive; no pathological reflexes were elicited. He had a moderate secondary anemia which responded well to iron therapy. The total white and differential counts were normal. The sedimentation rate was 24 mm. in one hour. By February it had dropped to normal. On March 7, 1947 the total blood proteins were 6.0 g., albumin 2.7 g. and globulin 3.3 g. Blood cholesterol was 215 mg. Repeated urinalyses were negative. All sputum examinations, including culture of a gastric lavage, failed to demonstrate tubercle bacilli. An X-ray film of his chest showed a normal right lung; the left lung field was homogeneously opaque up to the level of the sixth rib posteriorly; several calcified deposits were present above this level. The homogeneous density was thought to be due to thickened pleura or possibly fluid. Repeated roentgenograms did not show any essential changes.

On January 30, 1947, 750 cc. of cloudy yellowish fluid were removed from his left chest. It contained many cholesterol crystals. Smears and cultures for pyogenic and acid-fast bacilli were negative; specific gravity was 1.023; no chemical analysis was done. During February and March, three aspirations were performed, and a total of 1,650 cc. of cloudy fluid was removed. The last specimen was orange colored; it had a specific gravity of 1.020; P_{H} 7.0; total cell count was 30 with 58 per cent neutrophils, 40 per cent lymphocytes and 2 per cent monocytes. Many cholesterol crystals were again present; cholesterol content was 185 mg.; total protein 3.3 g.; albumin 2.1 and globulin 1.2, making an albumin-globulin ratio of 1.75. According to Moll and Fowweather's (2) experimental conclusions, a ratio of greater than one indicates that the fluid has a tendency to dissolve cholesterol. This was not borne out by the next aspiration which was performed on April 4, 1947, when 500 cc. of cloudy orange-red fluid with a golden yellow siccum were obtained with a specific gravity of 1.018, and an alkaline reaction. Total cell count was 15,200 with 84 per cent neutrophils and 16 per cent lymphocytes. The dissolved cholesterol was 177 mg., total protein 5.7 g., albumin 2.7 g. and globulin 3.0 g., making an albumin-globulin ratio of 0.9. Cholesterol crystals were present in large numbers. Irritation of the pleura had apparently resulted in an outpouring of protein and cells. The albumin-globulin ratio had become reversed, mainly due to an increase of globulin. However, no increased cholesterolysis was noted. All aspirations had revealed that the pleura had become markedly thickened and hardened.

The patient's course in the hospital was uneventful. He gained 20 pounds during his hospital stay and felt well. He never complained of any discomfort due to the fluid in his left chest but had a peculiar liking for aspirations. It was decided that his pulmonary tuberculosis was inactive and that no surgery was indicated to obliterate the left pleural cavity which continued to fill with fluid. He was discharged in good condition on April 4, 1947.

SUMMARY

A case of cholesterol pleural effusion is presented in a middle-aged male whose illness began with pulmonary tuberculosis and development of fluid in the left pleural space twenty-four years ago, from which he had no discomfort. The blood cholesterol was normal and the pleural fluid was sterile and contained about 180 mg. of dissolved cholesterol and innumerable cholesterol crystals. The pleura had become markedly thickened and hardened over the years.

SUMARIO

Derrame Pleural de Colesterol

Preséntase un caso de derrame pleural de colesterol en un varón de edad mediana cuya enfermedad comenzó con tuberculosis pulmonar y formación de líquido en el espacio pleural izquierdo sin experimentar entre tanto malestar. La colesterinemia era normal y el líquido pleural estéril, conteniendo unos 180 mg. de colesterol disuelto y un sinnúmero de cristales de colesterol. En el transcurso de los años la pleura se había espesado y endurecido notablemente.

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MEDIASTINAL EMPHYSEMA FOLLOWING THORACOSCOPY

A Case Report

IRWIN G. KARRON¹

Although many cases of mediastinal emphysema have been reported, its occurrence following thoracoscopy is rare. Macklin (1) reviewed the literature in 1944 and found only the case reported by Hernandez and Brea (2); I have searched the literature since that date and can find no other cases.

Hernandez and Brea reported a 49-year-old white male who had a spontaneous pneumothorax due to fibroid tuberculosis. This pneumothorax was maintained therapeutically, but was unsatisfactory because of adhesions. Thoracoscopy was performed, but lysis was not feasible because of the multiplicity of the adhesions. Ten hours following the operation the patient first noticed subcutaneous emphysema of his neck. This became extremely severe during the next eleven hours. He developed intense cyanosis, dyspnea, cardiac collapse and died. A diagnosis of mediastinal emphysema was confirmed by autopsy.

The case to be reported here is of interest chiefly because of the X-ray findings and because the pneumothorax was successfully maintained in spite of massive intrapleural hemorrhage.

This patient was a 30-year-old white soldier whose symptomatic onset of tuberculosis occurred in Burma in March, 1945. At that time he had a caseous infiltration in the right second anterior interspace, with a small central cavity. Subsequent overseas films showed an increase in both the excavation and the pericavitary infiltration. He was evacuated to the United States and transferred to Bruns General Hospital, an Army Chest Center. His film of December 6, 1945 revealed an irregular cavity, 4 x 3 cm., with a fluid level at the level of the right second anterior rib, with infiltrations extending down to the fourth rib. The heart and the remainder of the lung fields were normal except for a calcified primary complex on the left side.

On strict bed-rest his cavity decreased to 1 cm. in diameter and the fluid level disappeared. However, because of the persistent cavitation and positive gastric cultures, a right pneumothorax was induced on February 8, 1946. The collapse was unsatisfactory because of several adhesions extending to the diseased area. Staff conference approved an attempt at pneumonolysis. The patient's bleeding and clotting times were found to be within normal limits.

On April 16, 1946 thoracoscopy was performed. A band adhesion extended from the right apex to the lateral chest wall. Its base was anesthetized transpleurally with novocaine, and the adhesion was severed at its chest wall attachment. This was complicated by a small amount of bleeding from the upper end of the adhesion which was controlled without difficulty by electro-coagulation, and the patient was returned to his ward at 10 a. m. At 11 a. m. he was given 30 mg. of codeine, and this was followed by vomiting and retching during the entire afternoon, probably a response to codeine. He became moderately dyspneic and air was removed from his chest.

The next day, April 17, he had a temperature of 100.4°F., pulse of 112 and 30 respirations per minute. He did not complain of any chest pain. The outstanding feature on

¹ Captain, M.C., A.U.S., Bruns General Hospital, Santa Fe, New Mexico. Present address: 1150 Grand Concourse, Bronx 56, New York.

physical examination was extremely wide-spread and severe subcutaneous emphysema involving the chest, back, neck, right arm, upper right thigh and scrotum. Dyspnea was slight and there was no cyanosis. The respiratory excursions of his chest were good bilaterally. Auscultation of his lungs was unsatisfactory because of the subcutaneous emphysema. Normal cardiac dullness was absent, but Hamman's sign was not heard.

A portable X-ray film on that day revealed that the right lung had reexpanded. There were large collections of fluid along the right lateral chest wall and at the right base. The mediastinal shadow was shifted about 3 cm. to the left. The pericardium was encased by a mantle of air about 1 cm. wide. A standard X-ray film on the following day, April 18, showed four separate collections of fluid: (1) extrapleural fluid along the lateral chest wall; (2) intrapleural fluid; (3) fluid within the mediastinum, with an air-fluid level; (4) a dense shadow in the right mid-lung field, probably representing encapsulated interlobar fluid. The first two of these fluid collections were found on aspiration to consist of blood. The mediastinal fluid was probably either blood or serous fluid produced by irritation of the mediastinum by air. The right diaphragm, previously normal in position, appeared to be elevated 6 cm. by what was believed to be an intrapulmonary pocket of blood. In order to prevent infection of these multiple blood pockets, intramuscular penicillin, 25,000 U every three hours, was started on that day. His temperature rose to 101.4°F. and he ran a low-grade fever of 100° to 101°F. during the next ten days.

On April 18 his pneumothorax was reinduced, and 400 cc. of air was given, the final pressure being -12 -10 cm. An X-ray film on the following day revealed a mantle pneumothorax. The patient was tapped for the first time on April 20, and 830 cc. of almost pure blood which did not clot was removed. This bloody fluid contained 9 g. of hemoglobin per 100 cc. The patient was given another pneumothorax refill of 400 cc., and 50,000 U of penicillin were injected intrapleurally as a prophylactic measure. The chest fluid was negative on smear and culture for both pyogens and tubercle bacilli. A transfusion of 500 cc. of whole blood was given on April 21. This was followed by an exfoliative dermatitis involving the skin folds between his toes which cleared in two weeks. On April 22 another 500 cc. of bloody fluid were removed by chest tap, and 50,000 U of penicillin were again injected intrapleurally. An X-ray film on April 24 showed that the intrapleural fluid had greatly decreased and that the mediastinal emphysema had persisted. An electrocardiogram on that day was entirely normal. His subcutaneous emphysema had almost disappeared by that time.

During the following week a total of 630 cc. of thin dark-brown fluid was removed from his chest, which was then irrigated with saline, the final irrigation containing less than 1 g. of hemoglobin per 100 cc.; 40,000 U of penicillin were injected intrapleurally (total intrapleural dose: 140,000 U).

On May 1 the lung still seemed to be broadly adherent to the parietal pleura. By May 13 the fibrinous pleural adhesions had thinned and stretched to 3 cm., and the mediastinal emphysema had disappeared. On June 4 there were only two fine adhesions visible, and they were not adjacent to diseased lung. The collapse was excellent, with cavity closure, and the intrapleural fluid had completely disappeared. The extrapleural pocket of blood had greatly decreased in size. The patient was discharged to the Veterans Hospital at San Fernando, California, and his pneumothorax has been successfully maintained at that institution.

It is of interest to note that although Hamman's sign was carefully sought it was never observed. The patient, after the first two days, was perfectly comfortable in spite of marked mediastinal emphysema as demonstrated on X-ray films. He had no pain, cardiac embarrassment nor electrocardiographic

abnormality. His mediastinal emphysema persisted for three weeks according to radiography and fluoroscopy.

SUMMARY

A patient is reported who, following pneumonolysis, developed mediastinal emphysema, accompanied by massive intrapleural and extrapleural hemorrhage. His pneumothorax was maintained and he recovered without ill effects.

SUMARIO

Enfisema del Mediastino consecutivo a una Toracosopia: Historia Clínica

El caso descrito es en un enfermo quien, consecutivamente a una pneumolisis, manifestó enfisema del mediastino, acompañado de hemorragias intra y extrapleurales masivas. Se mantuvo el neumotórax y el sujeto se repuso sin efectos contraproducentes.

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HOME SUPERVISION OF THE TUBERCULOUS¹

P. K. TELFORD

Each evidence of decline in the morbidity of tuberculosis stimulates anew the efforts of public health workers to discover practicable means for complete final eradication of the disease. Isolation of open cases such as has been accomplished in leprosy is not likely to be possible soon enough to be of any interest to us at this time, and also the necessity for it is quite doubtful.

The characteristics of contagion in tuberculosis must be carefully adjudged in establishing a program of isolation. The only specific precedent we have is the virtual elimination of tuberculosis in cattle by destruction of infected animals. This is convincing evidence that human tuberculosis can be stamped out when all sources of new infections can be segregated. The effectiveness of segregation has been proved but devising means of utilizing this principle in human infections is the remaining problem.

The premises having been established that human tuberculosis is an infectious disease and its spread can be completely stopped by controlling infected cases; that complete isolation of infected cases is not practicable; there must be instituted, if possible, a degree of isolation that can be reasonably expected to be effective and still be within the limits of practicability. The Los Angeles County Health Department, in coöperation with the Los Angeles County Charities Department, conducted an experiment in this field, beginning December, 1932, that is pertinent to a solution of the problems involved. Speaking of the need for isolation of all known cases, Frost (1) said, "It is also one of the measures at present often neglected or compromised by makeshift attempts at home isolation." Our experiment was designed to be more than a makeshift, and to approach the effectiveness of sanatorium isolation as nearly as practicable. These efforts also contributed materially to improving the living and social conditions in tuberculosis families which is a known factor in limiting spread of the disease.

This attempt to accomplish adequate isolation in the home was justified from a number of viewpoints. In keeping open cases at home that had received maximum benefit from sanatorium treatment, or not in need of institutional care other than for isolation, more sanatorium beds were made available to those needing specific treatment. The degree of contagiousness of tuberculosis being slight, the means of preventing spread from a confined patient are relatively simple. The patient and family are more contented with the patient at home. The cost was expected to be much less than sanatorium care, and this experiment proved to be a great public economy. The desirability of an improved plan for home care could not be questioned but the effectiveness and practicability of the proposed plan needed demonstration.

¹From the Los Angeles County Health Department, 803 North Spring Street, Los Angeles 12, California.

This reasoning persuaded county administrators to provide the necessary funds and employee time for a demonstration. The Charities Department designated a worker to spend as much time as needed on the project with a sum of money set aside immediately available for necessary purchases. Health Department workers, doctor, nurses, nutritionist, social worker, quarantine officer and sanitation inspector, were assigned to the work as required. These people then met and organized the work.

The first task of this group was to choose a site for the experiment. They selected a small, compact, more or less isolated Mexican neighborhood where a tuberculosis problem existed. It consisted of about two square city blocks with railway tracks on the west, a boulevard on the east, and a sparsely settled surrounding territory. In this situation there were 7 patients with active reinfection type tuberculosis, 2 far advanced, 5 moderately advanced; one patient with active primary infection; 3 cases with arrested reinfection type tuberculosis; and 6 children previously recommended for preventorium care. Two of the cases with active pulmonary tuberculosis had been in tuberculosis rest homes, and arbitrarily returned home against advice because they would rather be at home. Related problems were stated in the original report of the welfare worker: "Sufficient information was obtained to conclude that all the vices and problems presented in a really large slum area were to be found in this little colony—bootlegging, prostitution, gambling, thievery, adultery, broken homes, illegitimate children, filth and ignorance—these and more were coupled with charming Mexican cordiality, friendliness and the sincere desire to help in developing the functions of the Community House." In this mission community house headquarters were established, including a clinical room and the simple requirements for holding classes in Americanization, sewing and cooking, which were used continuously throughout the period of about a year and one-half while the intensive program continued.

It is pertinent to question how successful such plans would be when applied to better homes. Certain modifications would be necessary to meet varied conditions found in better homes. However, it is first necessary to demonstrate a program effective where most of the cases are, and where by far the greatest danger of contagion exists. When this is accomplished there will be a basis on which to formulate modified plans to meet the needs of any situation. The neighborhood in this study was one of the worst type.

The congestion of the neighborhood in which these cases resided is shown by the census. There were 323 individuals in 63 families. The houses and shacks lined the streets and the alleys with many in between covering most of the ground area. A complete medical, social and sanitary survey was made and an analytical tabulation of this information is available, but these details will not be given here. A physical examination was made on 276 persons, including 113 Mantoux tests with X-ray films of the 30 reactors; and on 41 adults Wassermann tests were done. Little new disease was discovered: one case with active primary infection, 2 cases with arrested reinfection tuberculosis and one patient with lues were found.

Following this preliminary work, attention was concentrated on the homes of active cases. Each patient was provided with an individual room equipped as similar to the sanatorium pattern as possible. Some old furniture and equipment were available from various sources, and necessary windows, screens, doors and lumber were supplied where necessary. A chicken wire gate with a hook was fitted to the connecting door in each house. The construction labor was done by the residents. Diets were supplemented as recommended by the nutritionist. The cooking classes also aided in teaching the families to make the most of the allowances granted them by the Welfare Department. Much of the success attained was through improving the living conditions. Also, in receiving additional food supplies and other aid, the people felt they were receiving some tangible reward for complying with the rules and regulations, and we secured cooperation far greater than in any previous experience.

The same equipment was supplied to ambulant patients with positive sputum and restrictions were modified only as deemed safe in each instance. The chief features of ambulant control were training in the use of tissues and pocket container, and avoiding indoor associations. Casual public contact is not the source of new disease, in our experience. Success in combating the danger from ambulant cases depended upon the same routine as applied to those confined, stressing the frequency of supervision by the various workers.

Because fifteen years have elapsed since the experiment began, it would seem theoretically possible to give a valuable report on the amount of spread that has occurred in these tuberculosis families after this length of time. Unfortunately, most of the families have scattered to the four winds. However, in 1934, when the special services were being terminated, about one and one-half years after their inception, no new cases had occurred, and there was no evidence of spread of infection to nonreactors in the supervised families. The whole community was resurveyed in May, 1934, and no new cases were found, except a moderately advanced case in a newcomer in a trailer camp close by. By 1936 it was found that, of the original 7 active cases, 3 died, 3 became arrested and one was deported to Mexico. One family moved into the colony with 2 active cases but was later deported to Mexico. Another family was transferred to the colony two weeks after the mother died of tuberculosis. This family included 2 moderately advanced cases and a baby with active primary infection. One of these cases was sent to a sanatorium for instituting pneumothorax treatment.

One of the patients who died had been a problem. Quarantine was necessary to control the patient. The family decamped and the police returned them after two months of search. The patient was then sent to a tuberculosis rest home under a legal isolation order. The disease being progressive, she was later sent home to die.

The therapeutic result in this group as a whole was satisfactory. Sufficient supervision was provided to ensure observance of the amount of rest prescribed by the physician. New cases received three calls per week by the nurse and occasional calls by social service, welfare and quarantine workers. At least one call each working day was made by some Health Department worker on each

active case. As a contrast to our previous experience with the usual occasional call, this frequent repetition and stressing of the instructions to the patient and the family were found effective beyond expectations.

Another gratifying result of this constant supervision has been the voluntary removal of all the lawless element of the neighborhood. Previous to our invasion the better element had frequently appealed to the police without any improvement of conditions. However, under so much official scrutiny the criminal disappeared.

The advantages in the use of such a program as this are largely empirical in such a short experience, and particularly unconvincing in the degree of prevention in such a chronic slow-blooming disease as tuberculosis. The enthusiastic approval of all of the trained public health workers engaged in the project, however, testified that improvements accomplished in the home care of open cases well repaid the additional effort and the apparent expense. A financial report by the Welfare Department covering expenditures on these patients from November, 1932 to December, 1933 itemizes \$969.45 expended. It states that the cheapest type of other care that had previously been recommended, preventorium for 6 children, and tuberculosis rest homes for the other patients, would have been \$5,370 for the same period, or \$4,300.55 more. If the patients had been in the sanatorium the cost would have been \$11,040.00, or \$10,070.55 more. Additional time of personnel spent on the project can only be estimated. The same persons were working in the same field previously, and they absorbed the more frequent calls by adjustment of other work in their general public health program. The best estimate possible by supervisors of the work is that during this same period of one year there was expended in additional time by nurses \$2,000, inspectors \$400, medical social worker \$200 and doctor \$300, or a total of \$2,900. This expense being included, the cost was then \$1,400 less than other care of the cheapest type available, and \$7,170.55 less than sanatorium care. As previously stated, there were many related functions performed but there was an average of 8 patients cared for in homes, who otherwise should have been in institutions. In the light of present studies for evaluation of the effectiveness of traditional public health supervision of those suffering from exanthematous diseases and the trend of thought toward restrictive modification of these functions, it is pertinent to predict more time will become available for tuberculosis. It is an uncontrovertible fact that tuberculosis causes more disability, death and public expense than all other communicable diseases combined, and that good public health procedure reduces its morbidity. When these two facts are joined, the sum may be expressed in the possibility of the proposed program being absorbed by an established health department with little or no additional personnel.

This experiment was not to demonstrate a cheaper method or a substitute for sanatorium care but to provide better home care for those who must or can remain at home and, at the same time, isolate them more effectively. It is felt that this added amount of supervision would nearly meet our needs for eradication of tuberculosis, and possibly meet them adequately. Frost (2) stated:

"However, the condition necessary for eradication of an obligate parasite is not that transmission be immediately and completely prevented, but that it be lowered and held permanently below the level at which a given number of infectious hosts succeed in establishing an equivalent number to carry on the succession. . . and it is not inherently improbable that the tubercle bacillus should be similarly exterminated as the result of human interference with its propagation." The barriers against spread of infection set up in this simple experiment might prove effective if adopted on a large scale.

At the conclusion of this demonstration in 1935, an official proposal was made to extend this program to this whole Health Department area. A detailed plan for each of our neighborhoods with tuberculosis problems was submitted to the administration. We failed to secure official approval for the plans. Consideration of the program is recommended again at this time because there is a serious local shortage of institutional beds for the tuberculous, and an added emergency due to a great influx of population. Many areas throughout the country have similar treatment and isolation problems. It is appropriate to report a method of improved home care that has been demonstrated as practicable as a supplement to the institutional program. It is also felt that more intensive supervision of active cases in homes is an important step in hastening eventual eradication of tuberculosis.

SUMMARY

The public health fight against tuberculosis must devise more effective supervision of active cases remaining in homes. A small experiment in intensive home supervision of tuberculosis is related. This experience indicates that effective home care of cases not in need of specific treatment in an institution may be accomplished simply and with less expense than might be expected.

Extending this type of field work will evolve the ideal procedure to fit the need.

SUMARIO

Vigilancia Domiciliaria del Tuberculoso

En su lucha contra la tuberculosis la sanidad debe buscar una vigilancia más eficaz de los casos activos que permanecen en sus casas. Relátase un pequeño experimento en intensa vigilancia casera de la tuberculosis, el cual indica que podría lograrse sencillamente y a menos costo de lo que se creería, la asistencia doméstica eficaz de los enfermos que no necesitan tratamiento específico en una institución.

La difusión de las obras de este género hará surgir el procedimiento ideal que se amoldará a la necesidad actual.

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A NEW TUBERCULOSTATIC ANTIBIOTIC FROM A SPECIES OF NOCARDIA¹

A Preliminary Report

E. W. EMMART

The production of tuberculostatic antibiotics by certain genera of the *Actinomycetes* was first recognized more than thirty years ago. In 1913, Vaudremer (1) obtained a tuberculostatic substance from the filtrates of the culture medium and the mycelium of *Aspergillus fumigatus*. In 1940, similar results were obtained by Zorzoli (2) both with *Aspergillus fumigatus* and *A. albus*. The tuberculostatic properties of *Aspergillus fumigatus in vitro* have more recently been verified by Soltys, 1944, (3) and Asheshov and Strelitz, 1945, (4). Two other genera belonging to the *Aspergillaceae* have also been reported by Kallos, 1945, (5) and Gerber and Gross, 1945, (6) as producing an active substance against the tubercle bacillus. Slight inhibition was also obtained from a crude extract of the culture medium of *Penicillium notatum* by Smith and Emmart (7) and the tuberculostatic activity of the filtrate of another genus of the *Penicillium* group has recently been reported by Miller and Rekate (8). Actinomycin obtained from *Streptomyces antibioticus* (9), streptothricin from *Streptomyces lavendulae* (10, 13), and streptomycin from *Streptomyces griseus* have been reported by various workers (11, 12, 13, 14, 15) as having some degree of inhibiting action against the growth of the tubercle bacillus *in vitro* and *in vivo*. The present report presents another mold of the family *Actinomycetaceae* which has active tuberculostatic properties.

NOCARDIA COELIACA

In March, 1944, the mold under consideration appeared as an air-borne contaminant in a single flask of Kirchner's medium which had recently been planted with *Mycobacterium tuberculosis* of the human A27 strain. Within a week the small explant of pellicle of the mycobacterium had disappeared under an overgrowth of pale pinkish mold which covered a considerable area of the surface of the flask. Subcultures from the original culture have shown that as the mycelium develops the upper surface becomes "capucine buff"² (16, plate III) in color and finally "auburn" or dark brown. The under surface of the young mycelium in a few days becomes "orange rufous" (16, plate III) darkening into a "Sanford brown" (16, plate II). The aerial hyphae may be white or tinged pink, appearing at first on marginal edges of the vegetative mycelium. As the culture ages, the medium is gradually colored dark brown by the secretions of the mycelium. When the fresh culture is planted from spores the second growth of spore-bearing hyphae appears in fourteen to twenty-one days as irregular patches of the mycelium.

¹ From the Division of Physiology, National Institute of Health, Bethesda, Maryland.

² All colors are expressed according to Ridgway: Color Standards and Color Nomenclature (16).

Mutant yellow substrain. Four months after the subculturing of the original air-borne contaminant a light orange colored mutant appeared in the flask containing the original brown strain. When this variant was isolated the vegetative mycelium was found to grow more rapidly than the brown strain, and the spore bearing hyphae were scarce. Secretions from the mycelium colored the culture medium at first light yellow then orange. Since the two substrains are readily recognizable by color they are referred to as the "brown" and "yellow" strains.

Growth and behavior of strain. Data on growth and behavior of the mold on various media, and the microscopic appearance and subsequent classification of the mold have been furnished by Dr. C. W. Emmons as follows:

- (a) *Glycerol agar:* On this medium the fungus produced a greatly wrinkled, heaped up colony dull brown over the surface which was moist in young cultures but in older cultures showed in some areas a scant white "bloom" indicating the development of a very sparse aerial mycelium. A narrow zone of white, very short aerial hyphae also bordered the entire colony, the margin of the colony being lobed and irregular.
- (b) *Horse meat infusion agar:* On this medium the growth was like that on glycerol agar except that the development of a short white aerial mycelium was more pronounced.
- (c) *Acid dextrose agar:* (Sabouraud's) On acid dextrose agar a dry, white, thin chalky colony developed, the brownish pigment characteristic of the strain was visible beneath the short aerial mycelium in many cultures.
- (d) *On cornmeal agar:* The growth was dry, white (pinkish in the case of the yellow mutant), thin and chalky.
- (e) *On glycerin potato plug:* The original isolate made a restricted, wrinkled brown colony. The mutant produced a colony similar except for its yellow color.
- (f) *On starch agar:* The growth was white, very scant, and the starch was not altered; gelatin was strongly liquefied; litmus milk slowly became slightly alkaline; indol was not produced and nitrate was not reduced to nitrite.

Microscopic observations: The microscopic appearance of the fungus was that of a *Nocardia* (19). The hyphae, which were 0.5 to 1 μ in diameter, branched freely. Septa were infrequent or difficult to see in the smaller hyphae, but were frequent in the large hyphae and in old cultures. No true conidia were produced, but the short aerial hyphae broke up into fragments 2 to 6 μ in length. In old cultures on glycerin agar many of the fragments were short and nearly spherical in shape, measuring approximately 1.5 μ in diameter. Neither the hyphae nor the hyphal fragments were acid-fast.

Identification of strain: The fungus when first examined had an obvious resemblance to the pathogenic species *Nocardia asteroides*, although there were recognizable differences. Its possible pathogenicity was therefore investigated. Guinea pigs injected with a heavy subcutaneous inoculation in the groin developed adenopathy at the site of inoculation which subsided after a week. When the animals were killed a month after inoculation no lesions were found and the fungus was not recovered in culture. In mice inoculated with large doses intraperitoneally, and in rabbits inoculated in the ear vein, no lesions were

found when the animals were killed one month later and the fungus was not recovered in culture.

Variability is a generally recognized phenomenon in *Nocardia* (17, 18), variants being readily isolated from most strains. These may vary in biochemical activity as well as in morphology and color. This variability makes the exact identification of these organisms very difficult. The fungus studied seems to resemble closely *Nocardia coeliaca* (Gray and Thornton) comb. nov. (Gray and Thornton (18)).

METHODS

(a) *Culture media*: The mold which grows best at 37.5° C. was at first maintained on Kirchner's medium.³ This medium was used in all preliminary cultures and as a diluent in determining the tuberculostatic activity of the crude filtrate, referred to arbitrarily as "filtrate I" to distinguish it from other filtrations made in the process of extraction of the active substance. Since the active substance in the crude, unpurified state was not destroyed by autoclaving, the cultures were routinely autoclaved five or nine weeks after planting. The mycelium was filtered off, the pH of the filtrate adjusted to 7.2 and the fluid passed through Seitz filters. Filtrate I, therefore, consisted of Kirchner's medium in addition to pigments and antibiotic substances produced by the mold.

In later experiments the culture medium was supplemented with 20 g. of sucrose per 1,000 cc. of Kirchner's medium. The mold can be maintained on Czapek's agar medium as modified by Dox and Thom as cited by Henrici (19), but the best growth was obtained on Johnson's culture medium for fungi (20). The growth of the mycelium was slow on this medium but the solid medium had the advantage of maintenance of the strain without frequent transfers. Growth of the mycelium was either valued from 0 to 4 on the area of the mycelium (charts 2 and 3) or by grams in weight of the mycelium (chart 6).

(b) *Methods of testing for tuberculostatic action*: In all experiments the tuberculostatic action of the samples of the different lots of the crude filtrates was determined by planting both the whole filtrate with tubercle bacilli of the A27 strain and the filtrate diluted with Kirchner's medium. Cultures of each concentration were carried in triplicate and the amount of growth of the pellicle of the tubercle bacilli observed every few days, and evaluated from 0 to 4, 4 representing the completely covered surface of the flask.

RESULTS

A. Antibiotic Action of Filtrate I in Kirchner's Medium

In eight preliminary experiments it was observed that when the crude sterile filtrate of the culture medium from *Nocardia coeliaca* was planted with tubercle

³ Kirchner's Medium:

Dibasic sodium phosphate.....	3.0 g.
Monopotassium phosphate.....	4.0 g.
Magnesium sulphate.....	0.6 g.
Sodium citrate.....	2.5 g.
Asparagin.....	5.0 g.
Glycerin.....	20.0 g.
Water (triple distilled).....	1000.0 cc.

Two cc. of 40 per cent sodium hydrate are added before sterilization to adjust the pH to 7.2. The medium is autoclaved at 10 lbs. pressure for twenty minutes.

bacilli of the A27 strain no growth occurred. In consecutive experiments filtrate I from different plantings of *Nocardia* was diluted with equal parts of Kirchner's medium and planted in triplicate the average rate of growth in 50 per cent the termination of each experiment was found to be less than half the growth of the filtrate in Kirchner's medium alone (table 1). A marked variation in potency of the filtrates occurs from experiment to experiment (table 1). In one experiment the filtrates in 50 per cent dilution gave complete inhibition, although the average growth of strain A27 in 50 per cent dilution in these experiments was 1.2. The potency of the filtrates also increased with the growth and thickening of the mycelium. Filtrates of high potency were obtained after six to nine weeks of incubation.

In table 2 the differences in the tuberculostatic action of filtrates obtained from *Nocardia* cultures after forty-two and sixty-one days of incubation are given in

TABLE 1
Inhibition of growth of *Mycobacterium tuberculosis* (A27 strain) in 50 per cent filtrate I

EXPERIMENT NUMBER	GROWTH OF A27 EVALUATED FROM 0.0 TO 4.0 (AVERAGE OF 3 FLASKS)			DURATION OF TEST EXPERIMENT	AGE OF NOCARDIA CULTURE BEFORE FILTRATION
	Control—100% Kirchner's medium	50 per cent Filtrate I in Kirchner's medium	Per cent inhibition in 50 per cent Filtrate I		
1					
2	3.2				
3	4.0	1.2			
4	4.0	1.6	62.5	days	
5	4.0	1.7	60.0	30	days
6	3.8	1.9	57.5	41	17
7	2.7	1.2	52.5	41	18
8	4.0	0.6	68.5	31	25
	3.6	1.5	77.2	38	27
		0.0	62.5	36	28
			100.0	38	32
				38	32
				38	38

detail. The growth of the pellicle of the tubercle bacilli in undiluted filtrate and in dilutions of 1 to 8 (12.5 per cent), 1 to 4 (25.0 per cent) and 1 to 2 (50 per cent) in Kirchner's medium are given. No growth was obtained in the undiluted filtrate from cultures 42 days old, slight to moderate growth in 50 per cent dilution, while dilutions of 12.5 and 25.0 per cent supported good growth (part 1). When a filtrate from cultures of sixty-one days of incubation was used no growth of the tubercle bacilli occurred in the undiluted filtrate, very slight in 50 and 25 per cent, and only moderate growth in 12.5 per cent (table 2, part 2). From the data presented in tables 1 and 2 it can readily be seen that the age of the culture has a direct bearing on the tuberculostatic potency of the filtrate. As has been commonly observed by other workers in the field of antibiotics, considerable variation occurs in the potency of the antibiotic substance from lot to lot. Accepting the definition of the unit as the amount of the antibiotic which will completely inhibit the growth of *Mycobacterium tuberculosis* (strain A27) in 1 cc. of medium, we have obtained lots of crude culture filtrate which range in

potency from 1 to 4 units per cc. Chart 1 shows the tuberculostatic action of various dilutions of the crude filtrate obtained from modified Kirchner's medium containing sucrose. Lots of the filtrate I having a value of 4 units completely inhibit the growth of the tubercle bacilli of the A27 strain in dilutions of 25 per cent in Kirchner's medium.

TABLE 2

Tuberculostatic action of various dilutions of filtrates from Nocardia coeliaca cultures of different ages

Part 1.

Tuberculostatic Action of Filtrate I from Experiment 357. Age of Nocardia culture 42 days. (Growth of A27 Pellicle Valued 0-4)

TIME IN DAYS	PER CENT CONCENTRATION OF FILTRATE IN KIRCHNER'S MEDIUM				
	0	12.5	25.0	50.0	100.0
5	1.1	1.0	0.3	0.3	0
10	1.4	1.3	1.1	0.1	0
13	1.6	1.4	1.3	1.1	0
17	2.8	1.6	1.4	1.2	0
20	3.4	1.8	1.6	1.3	0
24	3.8	2.4	1.9	1.3	0
28	3.9	3.2	3.2	1.3	0
31	4.0	3.9	3.8	1.3	0

Part 2.

Tuberculostatic Action of Filtrate I from Experiment 375. Age of Nocardia culture 61 days. (Growth of A27 Pellicle Valued 0-4)

TIME IN DAYS	PER CENT CONCENTRATION OF FILTRATE IN KIRCHNER'S MEDIUM				
	0	12.5	25.0	50.0	100.0
7	1.3	1.0	0.2	0	0
10	1.3	1.1	0.4	0	0
14	1.4	1.1	0.6	0.1	0
18	1.5	1.2	0.6	0.1	0
22	1.6	1.2	0.6	0.2	0
25	1.8	1.3	0.7	0.2	0
28	2.3	1.3	0.7	0.2	0
32	2.8	1.3	0.7	0.2	0
35	3.5	1.3	0.7	0.2	0
37	3.9	1.3	0.7	0.2	0
42	4.0	1.4	0.7	0.2	0
45	4.0	1.4	0.7	0.2	0

B. The Effect of Filtrate I on Different Strains of Tubercle Bacilli

Although the virulent human strain A27 has been routinely used as a test organism, the crude filtrate is also active in dilutions of 25 per cent in Kirchner's medium against the strain H37Rv, the human strain A32 and the bovine Ravenel strain. These are relatively slow growing strains. When the antibiotic was

used in this dilution it was not found active against the rapidly growing avian strain 36 and 9077, the bovine S420, nor the human strains 279 and 607. The last four strains completely covered the surface of the flask within a week (table 3).

C. Difference in Growth Rate and Production of the Tuberculostatic Substance of the Brown and Yellow Strains

The yellow strain of *Nocardia coeliaca* which appeared as a mutant from the original brown strain differs not only in color but also in the rate of growth.

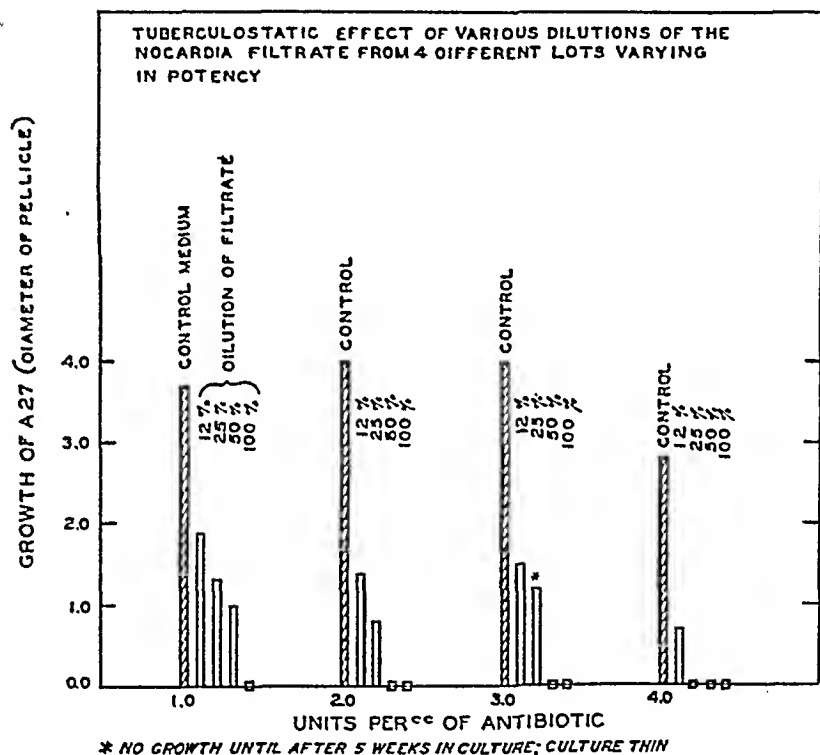


CHART 1. Variation in potency of different lots of filtrate I from *Nocardia coeliaca* cultures.

When the two strains were planted on Kirchner's medium and the amount of growth of each observed it was found that the mycelium of the yellow strain covered the surface in fifteen days, while it took thirty days for the brown strain to produce a mycelium of similar size (chart 2, part 1).

The culture media from these two substrains of *Nocardia* were pooled separately, the pH adjusted to 7.2 and filtered through Seitz pads. The filtrates were diluted 50 per cent with Kirchner's medium and planted with tubercle bacilli. When the growth rates of the pellicle of tubercle bacilli in the two filtrates were compared it was found that complete inhibition was obtained with 50 per cent

dilution of the brown strain, while 50 per cent dilution of the filtrate from the yellow strain permitted moderate growth (chart 2, part 2).

In order to determine whether or not utilization of the nutrient elements during growth of the *Nocardia* might be responsible for the inhibition of growth of the tubercle bacilli, the control medium was diluted with equal parts of water and the degree of growth of the tubercle bacilli noted. As is shown in chart 2 (part 2) and chart 5 (curve A) the growth rate of the tubercle bacillus was not markedly affected by this dilution. The inhibition of the growth of the tubercle bacillus in the cultures containing the filtrate could not therefore be accounted for by a possible deficiency of nutrient elements of the culture medium.

TABLE 3

The growth of various strains of Mycobacterium tuberculosis in 25 per cent Nocardia filtrate

STRAIN	GROWTH OF PELLICLE (0-4)		AGE OF TUBERCLE BACILLI CULTURE IN DAYS
	25 per cent filtrate (Average of 6 flasks)	Control medium (Average of 6 flasks)	
A27 (var. <i>hominis</i>), Slow growing strains.....	0.3	3.8	42
H37Rv (var. <i>hominis</i>), Slow growing strains.....	0.8	4.0	35
A32, Slow growing strains.....	1.3	3.4	42
Ravenel (var. <i>bovis</i>), Slow growing strains.....	0.6	2.8	34
#36 (var. <i>avian</i>), Rapid growing strains.....	4.0	4.0	27
#9077 (var. <i>avian</i>), Rapid growing strains.....	4.0*	4.0	6
#8420 (BCG-var. <i>bovis</i>), Rapid growing strains.....	4.0	4.0	6
#279 (var. <i>hominis</i>), Rapid growing strains.....	4.0	4.0	6
#607 (var. <i>hominis</i>), Rapid growing strains.....	4.0	4.0	6

* Average of 3 flasks.

D. Effect of Adding Sucrose to the Culture Medium

It has previously been shown that the addition of certain sugars to the culture medium greatly enhances the growth of various species of molds (21). In an attempt to increase the rate of growth of *Nocardia coeliaca* and the subsequent production of the antibiotic substance, sucrose was added in 2 per cent concentrations to Kirchner's medium. For comparison, control cultures without sucrose were maintained simultaneously. The data were obtained from five experiments set up in triplicate. The curves in chart 3 represent the mean rates of growth of the mycelium in medium containing no sugar (B) and in similar medium containing 2 per cent sucrose (A). In each experiment growth was consistently better in the flasks containing sucrose than in the flasks containing Kirchner's medium alone (chart 3).

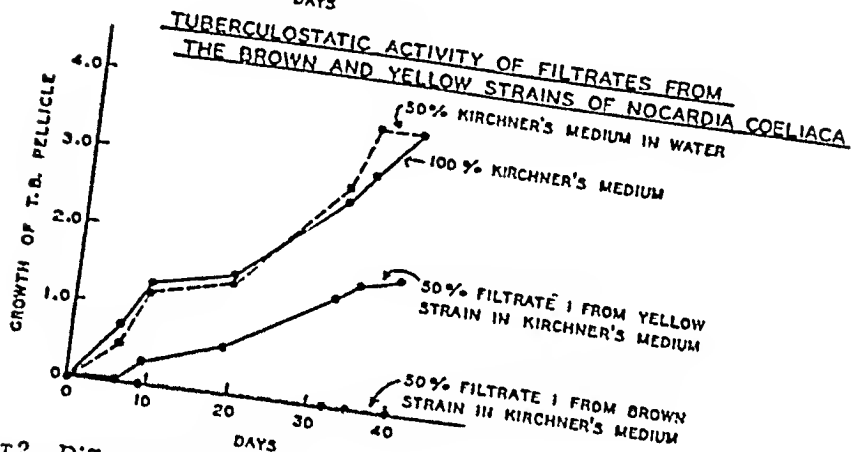
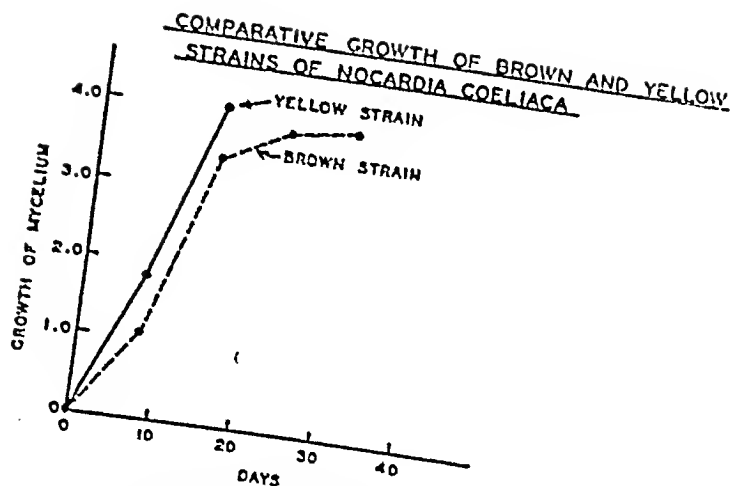


CHART 2. Difference in growth rate and tuberculostatic activity of the brown and yellow strains of *Nocardia coeliaca*.

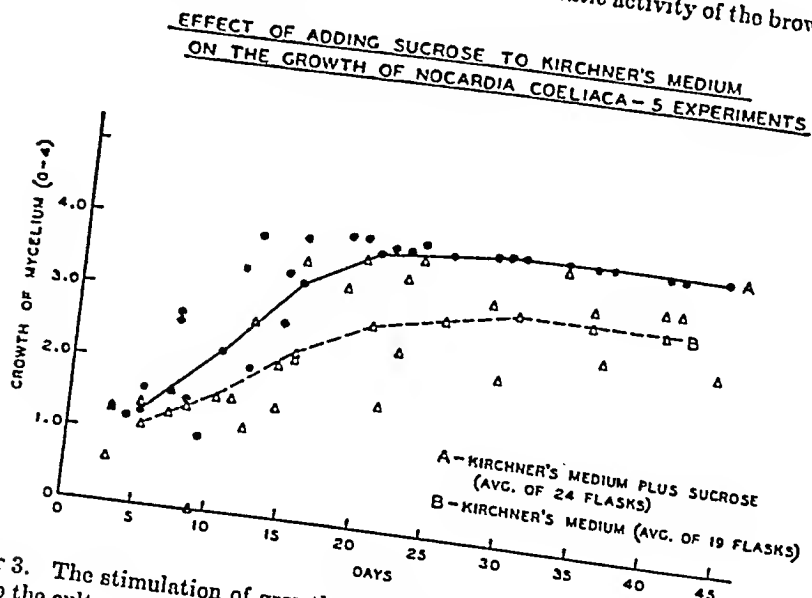


CHART 3. The stimulation of growth of *Nocardia coeliaca* by the addition of 2 per cent sucrose to the culture medium.

A comparison of the tuberculostatic action of the filtrates from cultures with and without sucrose in dilutions of 12.5, 25.0 and 50.0 per cent in Kirchner's medium as well as in the undiluted filtrates indicates that the tuberculostatic action is greater in filtrates from *Nocardia* cultures grown in the medium containing sugar than when grown in Kirchner's medium alone (chart 4).

In addition, if the time of onset of growth of the tubercle bacillus is taken into consideration, filtrates from medium containing sucrose completely inhibit growth in concentration of 50 per cent for two weeks or longer, while growth is present a few days after planting in filtrates from medium containing no sugar (chart 5).

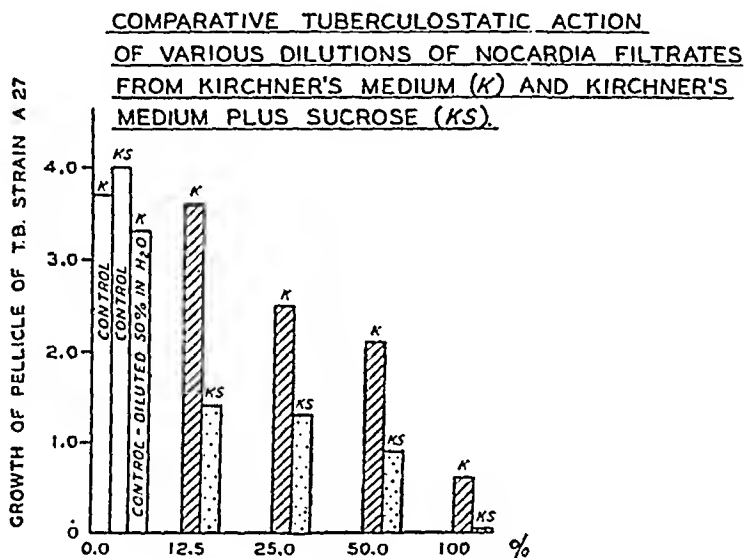


CHART 4. Showing in serial dilution in Kirchner's medium the increased tuberculostatic action of filtrate I from medium containing sucrose as compared with filtrates from Kirchner's medium alone.

E. The Effect of Different Sugars

(a) On the Growth of *Nocardia coeliaca*

(b) Upon the Production of the Tuberculostatic Substance

(a) Since it was found that sucrose not only increased the growth rate of *Nocardia* but also increased the production of the antibiotic substance, an attempt was made to use other sugars in place of sucrose with the hope of producing more rapid growth of the mold cultures. Various lots of modified Kirchner's medium were therefore prepared with the following sugars in concentrations of 2 per cent. The pH of these was adjusted to 7.2 and autoclaved at 10 lbs. pressure for twenty minutes. These sugars were as follows: crude commercial corn steep liquor (containing a mixture of sugars), fructose, lactose, raffinose, dextrose, sucrose, maltose, trehalose, galactose, melibiose, melezitose, honey dew honey, turanose,

d-xylose, cellobiose and d-glucoheptose.⁴ Kirchner's medium without sugar was used as a control. Spores from 5-day-old cultures were used to seed the flasks. The average growth from three flasks was based on the wet weight of the mycelium after the filtrate was pressed out. When the growth of the mycelium in the various sugar containing media was compared with that of the control medium, it was found that crude corn steep liquor and fructose gave the best growth, with lactose, raffinose, dextrose, sucrose, maltose, trehalose, galactose, melibiose, melezitose and honey dew honey following in consecutive order. Growth of the mycelium of *Nocardia* was inhibited when either turanose, d-xylose, cellobiose or d-glucoheptose was added to the culture medium (chart 6).

(b) In order to test the tuberculostatic action of the filtrates of these cultures, the pH of the crude filtrates was adjusted to 7.2 and the media sterile filtered and

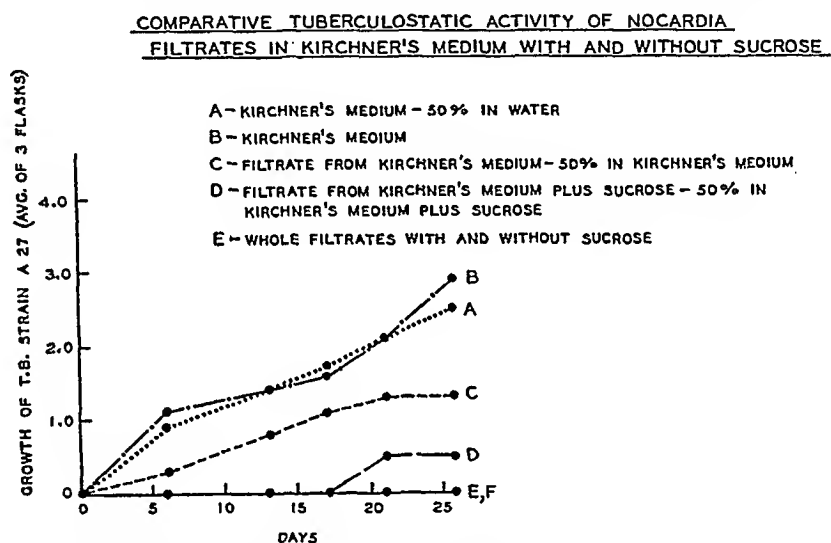


CHART 5. Showing the inhibiting effect of filtrates from culture medium with and with out sucrose in relation to time of onset and rate of growth of tubercle bacilli (strain A27) *in vitro*.

tested without dilution and in dilutions of 50 per cent, 25 per cent and 12.5 per cent in Kirchner's medium. The results showed that although a sugar might be effective in stimulating growth of the mycelium it did not necessarily follow that it stimulated production of the antibiotic. The order of effectiveness of the various sugars in the production of the antibiotic substance was as follows: trehalose, corn-steep liquor, lactose, dextrose, sucrose, d-glucoheptose, honey dew honey, d-xylose, maltose, galactose, melibiose, melezitose, cellobiose, turanose and fructose. It is of special interest that trehalose which is found normally in Baker's yeast and mushrooms and which stimulates only slightly the growth of the mold

⁴ We wish to acknowledge our indebtedness to Dr. Nelson K. Richtmyer of the Division of Chemistry of the National Institute of Health for his suggestions and coöperation in securing the various sugars used in these experiments.

GROWTH OF *NOCARDIA COELIACA* IN KIRCHNER'S MEDIUM AS AFFECTED BY THE ADDITION OF VARIOUS SUGARS

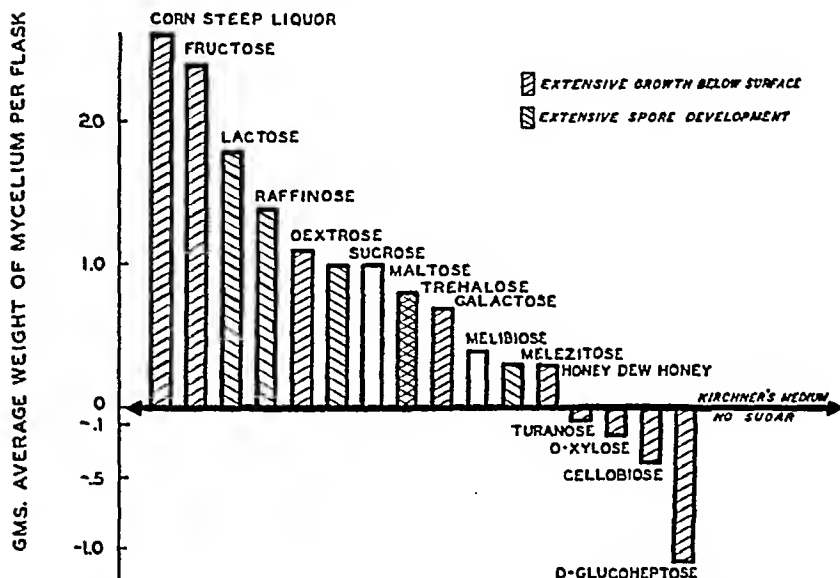


CHART 3. Showing the average growth of *Nocardia coeliaca* after forty days in Kirchner's medium containing 2 per cent of various sugars. Growth is represented in grams (average weight per flask of the mycelium).

TABLE 4

Effect of various sugars on tuberculostatic action of culture filtrates from *Nocardia coeliaca* vs. the tubercle bacillus (strain A27)

SUGAR	CONCENTRATION OF FILTRATE			
	12.5%	25.0%	50.0%	100.0%
Area of growth of pellicle of A27 at 37.5°C., valued 0- to 4+, after 40 days' incubation				
Trehalose.....	+	0	0	0
Corn steep liquor.....	+	+	0	0
Lactose.....	+	+	0	0
Dextrose.....	+	+	0	0
Sucrose.....	+	+	±	0
D-glucoheptose.....	++	+	0	0
Honey dew honey.....	+	+	+	0
D-xylose.....	+	+	+	0
Maltose.....	++	+	+	0
Kirchner (No sugar).....	++	+	+	0
Galactose.....	+++	++	+	0
Melibiose.....	++++	+++	+	0
Melezitose.....	+	+	+	+
Cellobiose.....	++++	++++	+	+
Turanose.....	+	+++	++	+
Fructose.....	++++	+++	++++	+

is the most active of these sugars in producing the tuberculostatic antibiotic. Nearly eight units per cc. of the tuberculostatic substance was obtained from culture medium containing trehalose. This was twice the amount obtained when sucrose was used (table 4).

F. Isolation of the Active Substance

Attempts to isolate and concentrate the active antibiotic substance from filtrate I by chloroform extraction or by dialysis through parchment membranes were unsuccessful. Continuous ether extraction followed by the removal of the ether by distillation and evaporation to dryness yielded a tuberculostatic substance of low potency. Purification of filtrate I by precipitation with ammonium sulphate was unsuccessful. The two methods which were finally adopted made use of both filtrate I and the mycelium.

(a) *Adsorption of the active substance from the filtrate by charcoal*: About 50 g. of charcoal (nuchar W) was added to each 5,000 cc. of filtrate I, shaken and allowed to stand for thirty minutes. The nuchar was then filtered off. When the remaining filtrate was tested for its tuberculostatic activity no inhibiting action was observed. Both the active substance and most of the coloring matter were adsorbed onto the charcoal. The charcoal was then eluted with equal parts of ether and 95 per cent alcohol and the eluate filtered free from the charcoal, evaporated to dryness and the residue weighed. The dark brown residue was water soluble. The pH of this dissolved eluate was readjusted to 7.2 and filtered through sterile centrifuge filters. The eluate fraction was then diluted in Kirchner's medium and the tuberculostatic action tested *in vitro*.

(b) *Extract of the mycelium*: In the second process in which the mycelium of *Nocardia* was used, the mycelium was filtered off, weighed and ground in equal parts of ether and alcohol. The brown ether-alcohol solution was then filtered free of the crushed mycelium, refiltered and evaporated to dryness. It was then weighed, dissolved in water to the desired concentration, the pH adjusted to 7.2 and the aqueous solution filtered through sterile centrifuge filters. The product extracted by ether and alcohol from the mycelium, contained a waxy substance which partially interfered with centrifugal filtration and in some preparations required greater dilutions and longer periods of filtration before all the extract could be passed through the centrifuge filters. It was also noted that extracts from the mycelium contained a substance which apparently affects the surface tension of the culture medium so that it did not support the weight of the pellicle of the tubercle bacillus on the surface of the culture. This interfered with the determination of the tuberculostatic action of such extracts, since in some cases it was necessary to dilute the extract to 0.02 per cent in order to permit the pellicle to remain on the surface. It is to be hoped that further concentration and purification of the active substance obtained from *Nocardia coeliaca*, will eliminate these difficulties.

In order to compare the tuberculostatic activity of the crude filtrate having a unitage of 2 with the charcoal eluate and the mycelium extract, the filtrate, the charcoal eluate and the mycelium extract were used in serial dilutions in cultures planted with tubercle bacilli and incubated simultaneously. Since the inhibition obtained in 25 per cent dilution of the filtrate I was 70 per cent while 60 per cent inhibition was obtained in 0.25 per cent of the concentrate of filtrate I, the con-

centrate may be said to be approximately 100 times more active than the crude filtrate (table 5).

In order to test the possible tuberculocidal action of filtrate I as compared with the charcoal eluate and the mycelium extract, the explant of the pellicle was removed from the *in vitro* cultures containing various dilutions of filtrate I and the tubercle bacilli planted on slants of Steenken and Smith egg medium (22). The growth which was observed every six days showed that explants of the pellicle of tubercle bacilli, which had been completely inhibited in 50 and 100 per cent of filtrate I, grew slowly on the egg media. This indicated that the action of filtrate I was tuberculostatic rather than tuberculocidal.

TABLE 5

Comparative tuberculostatic action of filtrate I, charcoal eluate and mycelium extract, strain A27

PER CENT CONCENTRATION	PER CENT GROWTH	PER CENT INHIBITION
A. Filtrate I		
0.00 (Control)	100	0
12.50	45	55
25.00	30	70
50.00	0	100
100.00	0	100
B. Norite eluate		
0.0 (Control)	100	0
0.5	85	15
0.10	95	5
0.25	40	60
0.50	20	80
C. Mycelium extract		
0.00 (Control)	100	0
0.05	100	0
0.10	97	3
0.20	50	50
0.25	40	60
0.30	40	60

The mycelium extracts and charcoal eluates were dried, weighed and dissolved in water and their activity tested *in vitro* in concentrations of .05, 0.1, 0.2, 0.3, 0.4 and 0.6 per cent. No growth occurred in flasks containing the mycelium extracts from 0.2 to 0.6 per cent and only slight growth occurred in dilutions of the charcoal eluates in concentrations of 0.4, 0.5 and 0.6 per cent. When the original explants were removed and transferred to slants containing Steenken and Smith egg medium no growth occurred on the slants inoculated with explants exposed to concentrations of from 0.3 to 0.6 per cent of mycelium extracts. However, slight growth occurred in slants planted from flasks which had contained 0.4, 0.5 and 0.6 per cent of charcoal eluate (table 6). This indicated that the action of the mycelium extract was tuberculocidal while the eluates from filtrate I were tuberculostatic.

TABLE 6
Tuberculocidal action of mycelium extracts as compared with the tuberculostatic action of eluates from charcoal adsorbates of filtrate I

CONCENTRATION OF MYCELIUM EXTRACTS AND ELUATES OF FILTRATE I		GROWTH OF TUBERCLE BACILLI, STRAIN A27				
Flask Number	Gram per cent	In flasks after 35 days (Growth valued 0 to 4)		Tube Number	After transfer of explants of tubercle bacilli to egg slants. (Growth values 0 to 4)	
		Mycelium extract	Eluate from charcoal adsorbate		From Mycelium extract	From eluate of Filtrate I
1	0.00	3.9	3.9	1	4+	4+
2	0.05	0.3	1.7	2	—	—
3	0.10	0.6	1.4	3	2	2+
4	0.20	0.0	1.1	4	1	3
5	0.30	0.0	1.2	5	0	2+
6	0.40	0.0	0.7	6	0	1
7	0.50	0.0	0.1	7	0	1+
8	0.60	0.0	0.2	8	0	1

G. The Tuberculostatic Action of Filtrate I and Mycelium Extracts in Bacillary Suspensions

(a) *The inhibiting action of filtrate I on the number of tubercles in the chorio-allantoic membrane of the chick:* In order to determine the inhibiting action of the crude filtrate on the production of tubercles in the chorio-allantoic membrane of the chick embryo, an inoculum was prepared from equal parts of the sterile filtrate having a potency of 2 units per cc. and a suspension of tubercle bacilli of the A27 strain. The dilutions were so made that 0.2 cc. of the suspension contained 1 mg. of tubercle bacilli and 0.2 units of the antibiotic substance. This was incubated for twenty-four hours at 37.5°C. and inoculated upon the chorio-allantoic membranes of 36 eight-day chick embryos as previously described (23, 24, 25). After six days the membranes were fixed *in situ*, excised and the tubercles counted. The average number of tubercles per membrane in the experimental groups was 8.4 and 16.8 in the control group.

(b) *The effect of bacillary suspensions containing filtrate I after injection into guinea pigs:* Parts of the suspensions used to inoculate the chorio-allantoic membranes were also used to inoculate guinea pigs. Part of the guinea pigs received the suspension after twenty-four hours' incubation and part after forty-eight hours' incubation. The guinea pigs were killed seven weeks after inoculation, and the amount of tuberculous involvement in the spleen, peritoneum, liver, omentum and lungs evaluated from 0 to 4. The total count for each animal was considered the index of tuberculosis. The weekly gain in weight was noted and the average gain or loss in weight was calculated. At the end of the first experiment the average gain in weight of the experimental group was 87 g., while that of the control group was 0.3 g. None of the experimental group had died while 5 of the control group were dead (chart 7, experiment 1). In the guinea pigs inoculated with a suspension incubated for forty-eight hours,

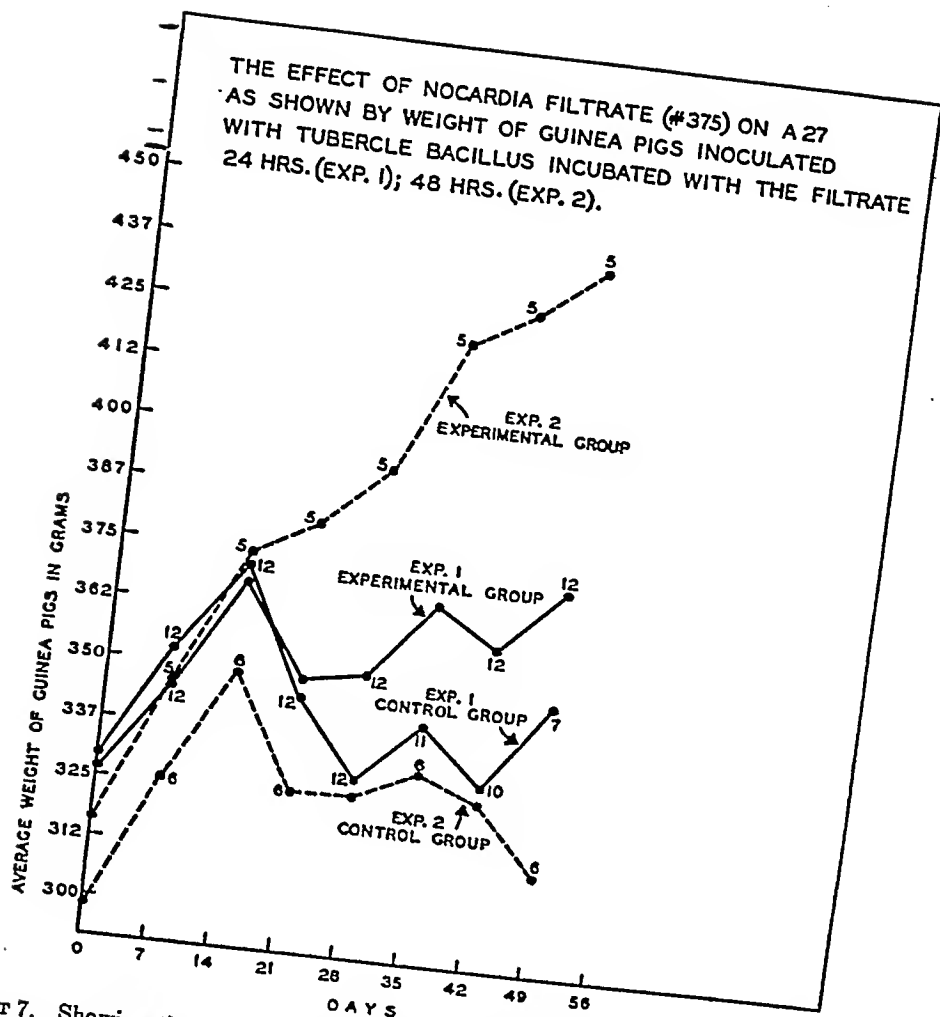


CHART 7. Showing the difference in weight curves of guinea pigs inoculated with a suspension of tubercle bacilli (strain A27) incubated with Nocardia filtrates for twenty-four and forty-eight hours, as compared with their respective control groups. Numerals indicate number of animals surviving.

TABLE 7

The tuberculostatic action of mycelium extracts on the production of tubercles in the chorio-allantoic membrane of the chick embryo

MYCELIUM EXTRACT LOT NUMBER	DOSE IN 0.2 CC. OF INOCULUM		NUMBER OF MEMBRANES INOCULATED	NUMBER OF EMBRYOS SURVIVED	AVERAGE NUMBER OF TUBERCLES PER MEMBRANE
	Mycelium Extract	M. tuberculosis Strain A27			
# 262	mg.	mg.			
	1.6	2	28	14	14
# 265	—	2	28 Controls)	13	23
	2.8	1	28	8	8
# 307	—	1	28 (Controls)	6	12
	2.4	1	30	7	2.2
	—	1	30 (Controls)	7	4.2

the average gain in weight was 23 g. in the control group against 93 g. in the experimental group. The experimental group showed a continuous increase in weight while the control group showed a rapid decline in weight after the onset of the disease (chart 7, experiment 2). These data suggest a more chronic type of infection in the experimental group as compared with the control group. Macroscopically no difference could be detected in the tuberculosis index of the two groups.

(c) *The tuberculostatic action of mycelium extracts on the chorio-allantoic membrane of the chick embryo:* The tuberculostatic action of mycelium extracts from 3 different lots was tested on the chorio-allantoic membrane of the chick embryo. The number of tubercles per membrane was counted and the average calculated. In each experiment the membranes inoculated with a suspension containing the tubercle bacilli and the extracts were found to have fewer tubercles than those of the control group (table 7). From these experiments *in vivo* it appears that the mycelium extracts have an inhibiting effect upon tubercle formation in the chick membrane.

SUMMARY AND CONCLUSIONS

1. A mold belonging to the family *Actinomycetaceae* has been isolated and classified as *Nocardia coeliaca* (Gray and Thornton) com. nov. Gray and Thornton.

2. The mold, which grows under the same experimental conditions as the tubercle bacillus, produces a tuberculostatic substance in the culture medium. This substance is thermostable and can be adsorbed on charcoal and eluted with equal parts of ether and alcohol. The dried brown extract is water soluble and tuberculostatic. It has been possible to obtain a concentrate approximately a hundred times more active than the filtrate. However, the method used at present removes only a small part of the substance present in the filtrate.

3. Extraction of an active water soluble tuberculostatic substance from the mycelium has been accomplished by trituration of the mycelium with equal parts of ether and alcohol.

4. The addition of sucrose to the culture medium increases the growth rate of the mycelium of the mold and the production of the tuberculostatic substance. Trehalose, while it does not markedly stimulate the growth of the mycelium, increases the production of the antibiotic substance. Filtrates of media containing sucrose were obtained with one to 4 units of the active substance per cc. while filtrates of media containing trehalose had a potency as high as 8 units per cc.

5. The crude filtrate in dilutions of 25 per cent was found to inhibit the growth of certain slow growing virulent human and bovine strains but this concentration was ineffective in inhibiting certain rapidly growing strains.

6. *In vivo* tests on the chorio-allantoic membranes of the chick embryo show that suspensions of bacilli of the A27 strain incubated twenty-four hours with the crude *Nocardia* filtrate produced fewer tubercles per membrane than the control

suspensions. When guinea pigs were inoculated with part of the same suspensions the weights of the animals indicated that the infection was of a more chronic type in the experimental group than in the control group.

7. Better methods of recovery and purification of the active substance are necessary before a sufficient quantity is available to treat infected animals and to compare its chemotherapeutic efficacy with other antibiotics.

SUMARIO Y CONCLUSIONES

Nuevo Antibiótico Tuberculostático de una Especie de Nocardia

1. Un hongo perteneciente a la familia *Actinomycetaceae* ha sido aislado y clasificado como *Nocardia coeliaca* (Gray y Thornton) com. nov. Gray y Thornton.
2. El hongo, que se desarrolla en las mismas condiciones experimentales que el bacilo tuberculoso, produce una sustancia tuberculostática en el medio de cultivo. Esta sustancia es termoestable y puede adsorberse en carbón vegetal y desleírse en partes iguales de éter y alcohol. El extracto pardo desecado es hidrosoluble y tuberculostático. También ha sido posible obtener un extracto concentrado unas cien veces más activo que el filtrado, aunque la técnica utilizada actualmente sólo elimina una pequeña parte de la sustancia presente en el filtrado.
3. La extracción de una sustancia tuberculostática hidrosoluble activa del micelio ha sido lograda por la trituración del mismo con partes iguales de éter y alcohol.
4. La adición de sacarosa al medio de cultivo acelera el desarrollo del micelio, y aumenta la producción de la sustancia tuberculostática. La trehalosa, si bien no estimula mayor cosa el crecimiento del micelio, acrecienta la producción de la sustancia antibiótica. Obtuvieronse filtrados de medios que contenían sacarosa con 1 a 4 unidades de la sustancia activa por cc., en tanto que los de medios que contenían trehalosa mostraron una potencia hasta de 8 unidades por cc.
5. El filtrado bruto a diluciones de 25 por ciento inhibió el crecimiento de ciertas cepas humanas y bovinas, virulenta, de desarrollo lento, pero esa concentración resultó ineficaz para inhibir ciertas cepas de desarrollo rápido.
6. Las pruebas *in vivo* en las membranas corio-alantoicas del embrión de pollo revelan que las suspensiones bacilares de la cepa A27, al ser incubadas por 24 horas con el filtrado bruto de *Nocardia*, produjeron menos tubérculos por membrana que las suspensiones testigos. Al inocular cobayos con una parte de las mismas suspensiones, el peso de los animales indicó que la infección era de tipo más crónico en el grupo experimental que en el testigo.
7. Se necesitan mejores técnicas de aislamiento y purificación de la sustancia activa para poder contar con una cantidad suficiente para tratar animales infectados y comparar su eficacia terapéutica con la de otros antibióticos.

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MEDIA FOR TUBERCLE BACILLI

RENÉ J. DUBOS AND GARDNER MIDDLEBROOK

In a number of recent publications, we have discussed the effect of serum albumin, of long chain fatty acids and of water dispersible esters of these acids on the viability and multiplication of tubercle bacilli (2, 3, 4, 6, 7). Further experience with these substances has led us to develop several culture media adapted to different types of bacteriological work. The object of the present paper is to describe the composition and properties of these media.

1. THE BASAL MEDIUM

The inorganic requirements of tubercle bacilli present nothing unusual. Mixtures of sodium and potassium phosphates provide a satisfactory buffer system. As in the case of other organisms, magnesium soon becomes a limiting factor of growth when large yields are desired. We have found iron requirements to be smaller than anticipated from published data. Other inorganic elements are required only in traces which are often present in sufficient amounts of tap water. Growth can be obtained between pH 5.5 and 8.2; however, initiation of growth appears to be optimum at slightly acidic reaction (pH 6.4 to 6.7). Despite the fact that the classical synthetic media advocated for the growth of tubercle bacilli contain extremely large concentrations of citric acid (15), we have failed to recognize any specially beneficial effect of this substance in our media. This may be due in part to the fact that the mixture of amino acids present in the casein digest, which we use as a source of nitrogen, substitutes for the 4-carbon-hydroxy acids. Furthermore, the favorable effect of citric acid in the classical media bears a definite relation to the state of the magnesium, calcium and iron ions in these media. As is well known, these 3 cations readily precipitate out of solutions, especially at slightly alkaline pH, whereas citric acid forms with them complexes which are stable in aqueous solutions. It is likely, therefore, that one of the chief beneficial effects of citric acid in the classical media is due to its ability to hold certain inorganic cations in solution. Since these cations, and particularly magnesium, may become limiting factors of growth, the rôle of citric acid in keeping them in solution is of particular importance where the value of the medium is measured in terms of its ability to yield large amounts of growth (as has been the usual practice in the case of synthetic media). It is worthy of notice that no precipitation should occur when the media to be discussed in the following pages are prepared according to the procedures described in this paper.

Glycerol or glucose are not necessary for initiation of growth in media containing enzymatic hydrolysate of casein. In consequence, these substances need not be a part of the basal medium. Where large yields of growth are desired, on the other hand, an abundant source of carbon and energy must naturally be supplied in the medium. Glucose or glycerol are satisfactory for this purpose. It is necessary to keep in mind, however, that autoclaving of

¹ From the Laboratories of the Rockefeller Institute for Medical Research, 68th Street and York Avenue, New York 21, New York.

glucose and of certain other carbohydrates at alkaline pH—especially in the presence of phosphate—results in the formation of caramelization products which are extremely toxic to the tubercle bacillus (6). No toxic effect is observed with glucose filtered or autoclaved at neutrality or acid pH and separately from the medium. When added to the latter in the form of a sterile solution, glucose appears as satisfactory as glycerol.

Although enzymatic digests of casein constitute a very favorable source of nitrogen for the growth of tubercle bacilli, acid hydrolysates are less satisfactory. Addition of tryptophane and of the common water soluble vitamins (even in the form of yeast extract) does not adequately supplement the acid hydrolysate of casein. It appears likely, therefore, that the enzymatic digests provide one or several factors—perhaps streptogenin-like (14)—which have not yet been identified. Asparagin appears to enhance the growth of a few strains of mammalian tubercle bacilli but is not an essential component of the medium.

Addition of water soluble vitamins, or of yeast extract, to media containing enzymatic hydrolysates of casein fails to increase the rate of growth or the final yield, or to decrease the size of the minimal inoculum required to initiate multiplication. On the other hand, there is present in serum (and in bovine plasma fraction V) a fraction soluble in ethanol which increases markedly the growth of tubercle bacilli. Increase of yield has also been observed upon addition of certain acetone and alcohol soluble extracts of hens' eggs and of plants. The substance or substances which are responsible for this favorable effect have not been identified. In a few cases, marked improvement of growth has resulted from addition to the medium of 0.005 per cent tocopherol phosphate, but the results have been too erratic to warrant detailed description at the present time. The basal medium can be conveniently prepared as follows:

KH_2PO_4
 Na_2HPO_4 , 12 H_2O
 Asparagin
 Add:
 Distilled water
 Enzymatic digest of casein*

1.0 g.
 6.3 g.
 1.0-2.0 g. } heat in 100 cc. distilled
 water to dissolve

850 cc.
 1-2 g. (20-40 cc. of a 5 per cent stock
 autoclaved solution in distilled
 water)

0.005-0.05 g.
 0.01 g. (1 cc. of a 1 per cent stock solu-
 tion in distilled water)

0.0005 g. (1 cc. of a 0.05 per cent stock
 solution in distilled water)

0.0001 g. (1 cc. of a 0.01 per cent stock
 solution in distilled water)

0.0001 g. (1 cc. of a 0.01 per cent stock
 solution in distilled water)

Ferrie ammonium citrate
 MgSO_4 , 7 H_2O

CaCl_2

ZnSO_4

CuSO_4

Adjust pH to 6.5 to 6.8.

Distribute medium in flasks or Blake bottles as described below, or in test
 tubes 25 mm. in diameter (5 cc. per tube).

* Two commercially available enzymatic digests of casein have been tested and found satisfactory, namely N-Z-Amine Type B (Sheffield Farms, 524 W. 57th Street, New York) and Bacto Casitone (Difco Laboratories, Detroit).

2. THE EFFECT OF THE SERUM ALBUMIN FRACTION

Most of our experiments have been carried out with bovine plasma fraction V (1) obtained in desiccated form from Armour Laboratories (Chicago, Illinois). This material has been compared for its effect on the viability and growth of tubercle bacilli with a number of different proteins including in particular whole serum, the different globulin fractions of serum and crystalline serum albumin (2). On the basis of these comparisons, it appears that the beneficial effect of serum albumin on the growth of tubercle bacilli can be analyzed in terms of two independent actions.

Bovine plasma fraction V (serum albumin) possesses to a remarkable degree the ability to protect tubercle bacilli against the bacteriostatic and bactericidal action of a variety of toxic agents (surface active substances including fats, fatty acids and their soaps; heavy metals and other inorganic cations; organic poisons such as phenols, quinones, etc.). This protecting effect is exerted also by crystalline albumin and is a property of the albumin protein. None of the other proteins tested exhibit the protective effect to a similar degree.

In addition to its protective effect, bovine plasma fraction V (serum albumin) exerts on the growth of tubercle bacilli an enhancing effect which is not exerted by highly purified preparations of crystalline albumin. This effect is not due to the albumin protein but to a heat stable component of serum (apparently soluble in alcohol) which has not yet been identified.

Naturally, the factors which determine the protective and growth enhancing properties of plasma fraction V are present in the whole serum. Unfortunately, many samples of serum also contain substances inhibitory to the growth of tubercle bacilli. Consequently, only those serum samples which are free of inhibitory effects can be used as growth adjuvants. None of the bovine albumin fractions so far tested have displayed any inhibitory action.

Sterilization of albumin can be achieved by filtration of a 5 per cent aqueous solution (in distilled water or 0.85 per cent sodium chloride) through bacteriological filters, preferably made of sintered glass or porcelain. Unfortunately, filtration allows occasionally the passage of small organisms which are not readily detectable by short term sterility tests but which contaminate subsequent cultures. It was called to our attention by Dr. R. D. Hotchkiss that, at acid pH (2.5 to 3.5), albumin can be heated without denaturation and without loss of its characteristic properties. In practice, heat sterilization of albumin can be achieved by addition to the solution of enough hydrochloric acid to adjust the pH to 2.5 to 3.5 (this requires approximately 1 cc. of 1 N hydrochloric acid per 10 cc. of 5 per cent albumin), heating at 90° C. for ten minutes, allowing to cool, and neutralizing with a sterile solution of sodium hydrate. A crude, but active preparation of albumin can also be directly prepared from serum by the following technique. To 10 cc. of bovine serum add enough hydrochloric acid to adjust the pH to 2.0 (approximately 1.5 cc. of 1 N hydrochloric acid per 10 cc. bovine serum); heat at 90° C. for ten minutes; remove the precipitate by centrifugation or filtration; neutralize with sodium hydrate; remove the new precipitate by centrifugation or filtration. Although the clear fluid thus obtained can be used

in lieu of albumin solution, it has not proved quite as effective in allowing the growth of small inocula.

3. OLEIC ACID

Long chain fatty acids, and oleic acid in particular, exert a dual effect on tubercle bacilli (4). On the one hand, their soaps have marked bacteriostatic and bactericidal action in most media. When supplied to the medium in a nontoxic form, on the other hand, they can act as nutrients for mycobacteria. Detoxification of oleic acid can be achieved by admixture of one part (by weight) of acid with 50 to 100 parts of albumin (also by weight); this corresponds to one mol of albumin per 4 mols of oleic acid. Interestingly enough, it is now known that starch can also neutralize the toxicity of fatty acids, although less efficiently than albumin (9, 13). This may account in part for the favorable effect of potato extract on the growth of tubercle bacilli.

Detoxification of oleic acid can also be obtained by esterification of the carboxyl group. However, ordinary esters are insoluble in water and therefore ill adapted to utilization by bacteria. The fact that the substances commercially known as Tweens consist of esters of long chain fatty acids which are completely dispersible in water accounts for their valuable properties to be discussed in the following chapter (3, 4, 6).

All strains of tubercle bacilli so far tested have been found to be able to utilize oleic acid, a property particularly striking in the case of avian strains but less readily demonstrated in the case of human and bovine strains (4). This difference is due to the fact that avian strains are fairly resistant to the toxic effect of oleic acid, whereas all human and bovine cultures are so susceptible to it that it is often very difficult to use concentrations sufficient to increase appreciably the amount of growth without reaching the toxic level. There is little doubt that the rôle of fatty acids in the metabolism of tubercle bacilli deserves more extensive study before its full significance can be evaluated.

4. WATER DISPERSIBLE ESTERS OF LONG CHAIN FATTY ACIDS

These substances are available under several trade names. Most of our experience has been gained with the polyoxyethylene derivatives of sorbitan esters distributed under the name of Tween by the Atlas Powder Company (Wilmington, Delaware). Of these, the ester of oleic acid Tween 80 has been used most extensively; it is readily dispersible in water in all proportions and stable to heat.

Tween 80 *per se* appears to be nontoxic for tubercle bacilli. Unfortunately, the commercial preparations are contaminated with small amounts of unesterified acid (0.6 per cent) which confer upon them the expected toxicity of long chain fatty acid; as already mentioned, this toxicity can be neutralized by addition of albumin (2). Tween can be purified by removal of the free acid, yielding a product which is entirely nontoxic for tubercle bacilli and which can be used to great advantage in the preparation of culture media. Unfortunately, aqueous solutions of Tween undergo very slow hydrolysis with release of some free acid; moreover, ordinary lipases (present in tissues, in bacteria and in most prepara-

tions of serum albumin) greatly accelerate the rate of hydrolysis.² For these reasons strains of mammalian tubercle bacilli which exhibit extreme susceptibility to traces of fatty acids (the Ravenel strain for example) may show delayed growth when very small numbers of cells are inoculated into Tween-containing media.

5. TWEEN-ALBUMIN MEDIUM FOR SUBMERGED-DISPERSED GROWTH

Tween 80 has the remarkable property of wetting the surface of tubercle bacilli and of thus rendering them dispersible in water (5, 7, 10). This is due to the fact that Tween becomes absorbed on the lipid portion of the bacterial surface through the long aliphatic chain of its molecule. The ethylene oxide chain of the ester thus forms a hydrophilic layer around the bacillus. Submerged and dispersed growth of all strains of tubercle bacilli so far tested can be obtained by adding 0.01 to 0.05 per cent of Tween 80 to the basal medium. The following medium is used in our laboratory for the maintenance of stock cultures and for the preparation of bacterial suspensions to be used in many different phases of experimental work *in vitro* and *in vivo*.

Basal medium
Tween 80

900.0 cc.

0.5 cc. (5 cc. of a 10 per cent stock solution in distilled water; keep this solution in the refrigerator and do not use after one month)

Autoclave
Add:

Albumin (bovine plasma fraction V)
Glucose

5 g. (100 cc. of a sterile 5 per cent solution)

5 g. (10 cc. of a 50 per cent stock solution in distilled water sterilized by autoclaving)

Inoculation of 5 cc. of this medium with 0.1 cc. of a fully grown culture in the same medium gives grossly visible growth within a few days. The culture of all avian strains is immediately abundant and diffuse; mammalian strains require an incubation time of several additional days for the growth to break up spontaneously into microscopic clumps and isolated cells. Undisturbed growth settles as a deposit in the bottom of the vessel; this deposit can be readily dispersed by gentle shaking. Repeated daily shaking increases the diffuse character of the growth and the rate of bacterial multiplication. Creeping of the growth up the side of the glass wall indicates exhaustion of the Tween. Cultures 7 to 10 days old contain per cc. about 0.3 to 0.4 mg. dry weight bacilli and 10⁹ living cells (as determined by inoculation of dilutions of culture into liquid media or on agar surface).

Cultures of virulent strains in this medium exhibit a high degree of pathogenicity. Papers describing the purification and chemical titration of Tween 80 will be published in the near future by B. D. Davis.

genicity for rabbits, guinea pigs, mice and chick embryos; graded amounts of inoculum can be prepared accurately by simple dilutions, thus avoiding the necessity of trituration prior to infection (5, 7, 12).

The density of these cultures can be measured directly by standard nephelometric methods; moreover, the medium lends itself to the enumeration of living cells by the dilution technique (inoculation of 10^{-8} cc. of 10-days-old cultures of H37Rv into a tube of new medium gives visible growth in ten to fourteen days). It is apparent, therefore, that the Tween-albumin liquid medium is well adapted to the quantitative study of the effect of nutritional factors and of bacteriostatic and bactericidal agents on the viability and growth rate of tubercle bacilli.

6. ALBUMIN MEDIUM FOR EXPERIMENTAL AND DIAGNOSTIC PRIMARY ISOLATION

In order to facilitate isolation of tubercle bacilli from material contaminated with other bacteria, it is advisable to render the medium as selective as possible by limiting the variety and concentration of the nutrients in the basal medium. This can be done, without affecting the initiation of growth of tubercle bacilli, by omitting entirely glucose and glycerine. It is also advisable for this purpose to reduce asparagin from 2 to 1 g., digest of casein from 2 to 1 g., ferric ammonium citrate from 0.05 to 0.005 g., per liter of medium. Optimum growth of tubercle bacilli is obtained at pH 6.5, a reaction which depresses the growth of many contaminants.

Dispersed growth (which is encouraged in the presence of Tween) is not necessarily an advantage for diagnostic work. We have observed, however, that virulent tubercle bacilli from pathological material (sputum, spinal fluid, infected tissues) inoculated into the casein digest-albumin medium for primary cultivation, always grow in the form of long strands which exhibit a characteristic pattern. These strands have a tendency to break up in the presence of Tween after prolonged incubation (two weeks) but persist for long periods of time in casein digest-albumin media, with or without added oleic acid, in the absence of Tween (11). Because of their large size, and characteristic morphology, they can be readily identified under the low power of the microscope, a property which naturally facilitates the search for the organisms in a suspected culture.³

The growth of all strains of avian tubercle bacilli is greatly enhanced by the addition of Tween or oleic acid to the medium but, as already mentioned, strains of mammalian bacilli vary greatly in this respect. In order to test the behavior of the bacilli present in pathological material toward oleic acid and Tween 80, we have inoculated a number of samples of tuberculous sputa and spinal fluids in parallel into the three following media.

(a) 90 cc. basal medium + 10 cc. of 5 per cent albumin

(b) 90 cc. basal medium + 0.2 cc. 10 per cent Tween 80 + 10 cc. 5 per cent albumin

(c) 90 cc. basal medium + 10 cc. oleic acid-albumin complex

³ Long strands of growth can be readily obtained from primary cultivation of pathological material in media containing 0.2 to 0.5 per cent albumin and 0.01 per cent Tween 80. Their morphology is illustrated in figures 1 and 2 (Ziehl-Neelsen technique).

The oleic acid-albumin complex was prepared as follows:

Dissolve 0.12 cc. of oleic acid (0.1 g.) in 10 cc. of N/20 sodium hydrate by shaking with rotary motion in a small flask.

Add 5 cc. of this solution to 95 cc. of a neutral 5 per cent solution of bovine plasma fraction V in 0.85 per cent saline.

Sterilize by filtration.

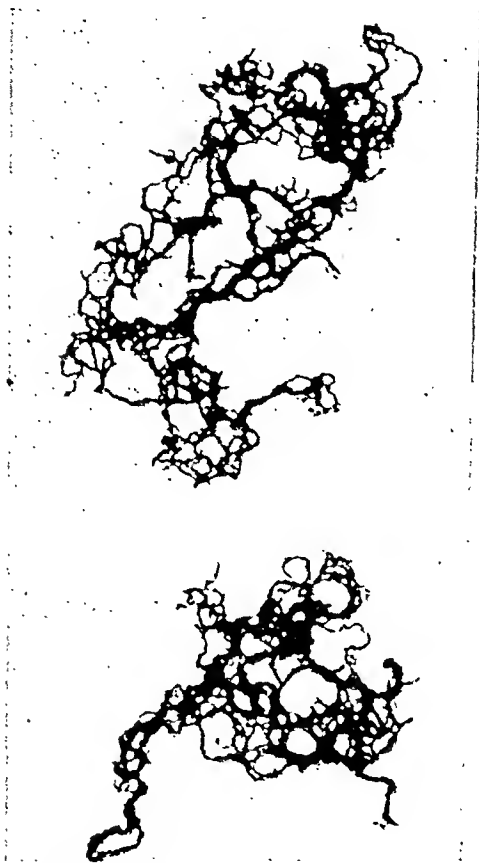


FIG. 1. Photomicrographs of Ziehl-Neelsen stained smear of intertwined "cords" of acid-fast rods in primary culture of sputum in Tween-albumin medium. The medium was inoculated twenty-one days previously with a small amount of the partially digested sputum of a tuberculous patient. $\times 155$.

The spinal fluids were inoculated directly into the liquid media (0.1 cc. of fluid per 5 cc. of medium). Sputa were treated with one-tenth their volume of N/1 sodium hydrate (giving a final concentration of N/10 sodium hydrate) and homogenized for thirty minutes by shaking. Samples of 5 cc. of this alkaline material were centrifuged for thirty minutes in the angle centrifuge, the supernates discarded, and the deposits collected in distilled water. Tubes containing 5 cc. of medium were inoculated with 0.1 cc. of the whole alkaline sputum, or with the centrifuged deposit from 5 cc.; it is worth noting that the high buffer

power of the medium made it unnecessary to neutralize the material before inoculation.⁴

It is not our purpose to compare the merits of the liquid casein digest-albumin media with those of the classical egg-yolk slants, for diagnostic purposes under practical conditions. Suffice it to say that fairly rapid growth of tubercle bacilli (seven to fifteen days) has often been obtained in the liquid media with sputa, spinal fluids and pleural exudates which had failed to reveal tubercle bacilli on direct microscopic examination (8). It is clear, therefore, that the casein digest-albumin media supply all the nutritional requirements of pathogenic myco-

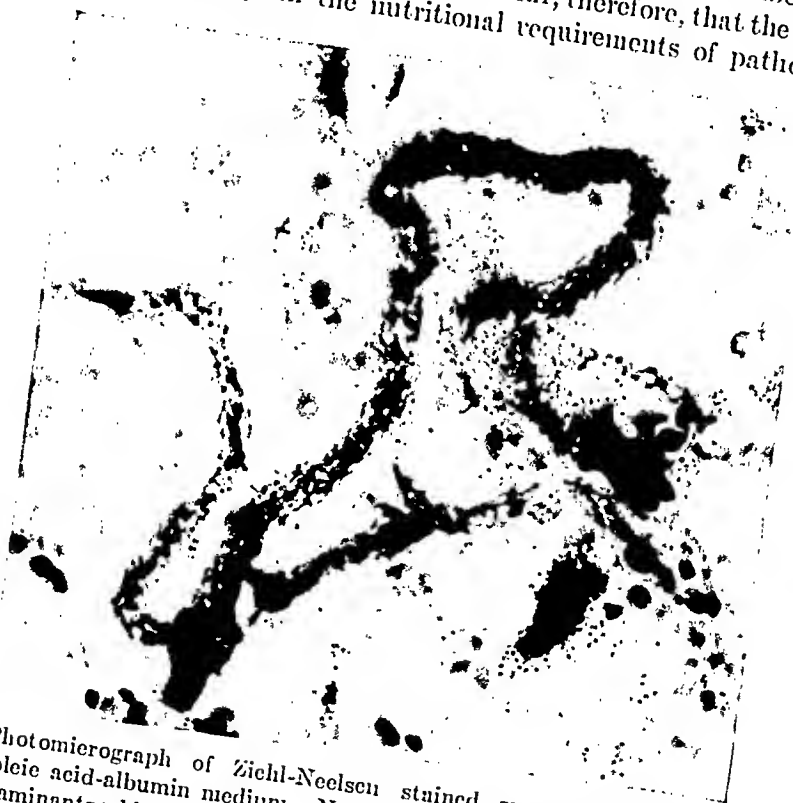


FIG. 2. Photomicrograph of Ziehl-Neelsen stained smear of primary culture of sputum in oleic acid-albumin medium. Note thick "cords" of acid-fast rods, and also coccoid contaminants which did not appreciably inhibit the growth of the tubercle bacilli.

bacteria even on primary cultivation. In addition to all avian strains, many mammalian strains are markedly stimulated by addition of oleic acid, or of Tween, to the medium. For example, one of these (Waller), isolated from human sputum, gave only very limited growth in the absence of these substances and could not be cultivated on two common types of egg media. We have not, so far, discovered any strain to be inhibited by either oleic acid (0.005 per cent) or Tween (0.01 per cent) on primary isolation from human pathological material. It is necessary to recall again, however, that two virulent laboratory strains

⁴ We wish to acknowledge with thanks the coöperation of Drs. Walsh McDermott and Susan Hadley, who supplied us with selected samples of human tuberculous material.

(the bovine culture, Ravenel, and the human culture, Jamaica) are unusually susceptible to the toxic effect of oleic acid, and that recovery of these cultures from the tissues of infected animals is most readily obtained in the albumin medium without addition of Tween or oleic acid.⁵ It would appear unwise, therefore, to formulate in final form the composition of media best adapted for diagnostic work until more is known of the growth requirements of the different strains of tubercle bacilli which occur in pathological material.

7. LIQUID MEDIA FOR THE PRODUCTION OF LARGE YIELDS OF MYCOBACTERIA BY SURFACE GROWTH

As in the case of other aerobic organisms, the final yield of tubercle bacilli in submerged cultures is limited by the rate of diffusion of oxygen through the liquid medium. It is obvious that increased oxygenation can be obtained by forced aeration or by mechanical agitation of the culture. It is also possible to increase enormously the yield of bacteria by resorting to the classical method of growth on liquid surface. Media which have been found useful for the utilization of this method will now be described.

Granted adequate oxygenation of the culture, the total yield of growth will naturally depend upon the concentration of nutrients. Among mineral constituents of the medium, magnesium and iron may become the limiting factors. The amount of iron supplied in the basal medium (0.05 mg. ferrie ammonium citrate per liter) is adequate for the production of a thin veil of growth. Increase of the concentration of the inorganic magnesium beyond 0.01 g. per liter is likely to result in the formation of a precipitate. This can be avoided by the simultaneous addition of citric acid which forms with magnesium ions a complex stable in aqueous solution. The following proportions are satisfactory for this purpose.

MgSO ₄	0.05 g. per liter of medium
Na ₂ Citrate	0.13 g. per liter of medium
The amounts of enzymatic digest of casein and of asparagin (2 g. per liter) provide sufficient organic nitrogen for large yields. Additional carbon as source of energy can be supplied in the form of glycerine or glucose.	
Basal medium	1000.0 cc.
Glycerine C.P.	7.5 cc.

* When working with glycerophobic strains, glycerine should be omitted and the glucose increased to 1.0 per cent final concentration.

The medium should be distributed in shallow layers (in Blake bottles for example). A ratio of surface area (in cm.²) to volume of medium (in cc.)

⁵ It is possible that the small amount of fatty acids known to contaminate plasma fraction V and the casein digest are sufficient to stimulate growth of these two strains without further addition of oleic acid or Tween.

corresponding approximately to unity appears optimum for utilization of nutrients.

The medium is inoculated with a seven to fourteen-day culture of tubercle bacilli in the Tween-albumin medium, described earlier in this report, using a ratio of one volume of inoculum to 40 or 50 volumes of the new medium. In order to initiate surface growth, the Blake bottles are allowed to rest on their sides for two days, during which time the bacteria multiply against the glass on the bottom of the undisturbed vessels. Then each bottle is tipped up and held in an upright position for three seconds; much of the culture remains clinging to the side of the bottle. When the bottle is returned to its horizontal position, small islets of organisms are floated onto the surface of the medium and serve to initiate a relatively rapid surface growth in the form of a pellicle.

By this technique the final amount of growth is, within limits, directly related to the concentration of magnesium in the medium. With 0.05 g. magnesium sulfate per liter, yields of 5 g. (dry weight) of bacilli can be regularly obtained within ten to fourteen days with the virulent form of the mammalian strain of H37.

8. SOLID AGAR MEDIUM

Agar exerts a pronounced inhibitory effect on the growth of tubercle bacilli. This is due, in part at least, to the fact that commercial preparations of agar contain long chain fatty acids which can be removed only with great difficulty by prolonged extraction with methanol (9). The toxic effect of agar on tubercle bacilli (as well as on other organisms) can be neutralized by addition to it of 0.5 per cent serum albumin (4). We have also observed that growth on agar requires concentrations of iron higher than those sufficient in liquid media; it appears that agar, or some product contaminating it, can bind iron in a form which is no longer available to the microorganisms for growth. The following medium has been devised on the basis of these considerations.

Basal medium	90 cc. (must contain 0.05 g. of ferric ammonium citrate per liter)
Agar (Difco)	1.5 g.
Autoclave, cool to 60° C.	
Add:	
Albumin	10 cc. of 5 per cent solution

It is convenient and economical to pour 12 to 15 cc. of medium into small petri dishes (5 cm. in diameter). The hardened agar surface can be inoculated with 0.05 to 0.1 cc. of adequate dilutions of a suspension of pathological material or of pure culture of tubercle bacilli. Growth of small inocula becomes visible ten days after inoculation (or earlier) and reaches maximum development in fifteen days.

The albumin agar medium can be modified by addition of Tween 80 or oleic acid. Tween-albumin agar is prepared by adding 0.01 to 0.05 per cent Tween to the basal medium prior to autoclaving, and oleic-albumin agar by replacing albumin by oleic-albumin complex (prepared as described earlier in this report).

In agreement with what is observed in liquid media, the growth of all strains of avian tubercle bacilli is markedly enhanced by the addition of oleic acid, or Tween, to agar media. As already mentioned, on the other hand, mammalian strains differ in their optimal requirements; some are somewhat inhibited by oleic acid (or Tween) whereas the growth of others is stimulated by these substances.

Direct growth of the bacilli present in human pathological material (sputa and spinal fluid) can be readily obtained on these agar media and evidence is accumulating that the method will prove useful for routine bacteriological diagnosis of tuberculous material. It is certain, however, that agar media can be used to advantage for enumeration of living tubercle bacilli by colonial counts. Of greater interest, perhaps, is the fact that they provide translucent substrates which lend themselves admirably to the study of colonial morphology and bacterial dissociation. Some of the results obtained by this method have been described elsewhere (11).

SUMMARY

On the basis of discussion of the effect of a number of substances on the growth of tubercle bacilli, descriptions are given of the composition and properties of different culture media adapted to the following purposes:

1. Submerged diffuse growth for experimental studies; in particular for the analysis of growth rates, for the detection and evaluation of antibacterial agents and for the infection of experimental animals.
2. Primary isolation from pathological material and quantitative enumeration of bacteria by the dilution method.
3. Production of large yields of bacilli in relatively short periods of incubation.
4. Growth on the surface of translucent agar media: for primary isolation, quantitative enumeration by colonial count, study of colonial morphology and of bacterial dissociation.

SUMARIO

Medios para Bacilos Tuberculosos

Tomando por base la discusión del efecto de varias sustancias sobre el crecimiento del bacilo tuberculoso, se facilitan descripciones de la composición y propiedades de diversos medios de cultivo adaptados a los siguientes fines:

1. Proliferación difusa sumergida para estudios experimentales; en particular para el análisis de los índices del crecimiento, para el descubrimiento y evaluación de agentes antibacterianos y para la infección de animales de experimentación.
2. Aislamiento primario del material patológico y enumeración cuantitativa de las bacterias por la técnica de la dilución.
3. Producción de grandes cosechas de bacilos en períodos relativamente breves de incubación.
4. Desarrollo en la superficie de medios transparentes de agar: para aislamiento primario, enumeración bacteriana por el recuento de colonias, estudio de la morfología colonial y de la disociación bacteriana.

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STREPTOMYCIN IN EXPERIMENTAL TUBERCULOSIS

The Effects in Guinea Pigs following Infection by Intravenous Inoculation
WILLIAM H. FELDMAN,¹ ALFRED G. KARLSON¹ AND H. CORWIN HINSHAW²

The favorable influence of streptomycin in opposing experimental tuberculosis in guinea pigs inoculated subcutaneously has been recorded previously (1, 2). Small to moderately large doses of fully virulent tubercle bacilli injected subcutaneously into guinea pigs do not immediately produce a widely disseminated tuberculous infection. Even though the infection following subcutaneous inoculation is permitted to progress for several weeks before treatment is begun, the extent and severity of the infection is much less than is true a few hours or a few days after inoculations by the intravenous route.

By the latter procedure there is produced at once a hematogenous dissemination of the infective bacilli which find lodgment in cellular elements throughout most of the parenchymal tissues. In these situations the bacteria proceed to multiply and promote a wide-spread miliary disease which is reseeded frequently by tubercle bacilli that enter the blood-stream from the numerous active foci. To modify favorably or to control such an infection should require a therapeutic substance of high potency. To determine whether or not streptomycin can cope successfully with experimental tuberculous infection established by intravenous inoculation of large doses of tubercle bacilli, the following study was done.³

METHODS

A group of 24 male guinea pigs having an average weight of approximately 500 g. were each inoculated by way of a superficial vein of the penis with 1.0 mg. moist weight of tubercle bacilli, strain H37Rv.⁴ The inoculated animals were caged in pairs and divided into three groups as follows: group 1, 12 animals, untreated controls; group 2, 6 animals treated with streptomycin beginning at once and continuing for sixty days; group 3, 6 animals, treated with streptomycin beginning on the fourth day after infection and continuing for 215 consecutive days. The daily amount of streptomycin administered per animal was 6 mg. given in four equal doses six hours apart.⁵

At the time of necropsy, tissues, including the brain and spinal cord, were removed for subsequent histological study. In addition a portion of the spleen from each animal was cultured for the presence of tubercle bacilli.

¹ Division of Experimental Medicine, Mayo Foundation, Rochester, Minnesota.

² Division of Medicine, Mayo Clinic, Rochester, Minnesota.

³ Corper and Cohn (3) observed the effects of streptomycin *in vivo* in a group of guinea pigs each inoculated intravenously with 1 mg. of a virulent strain of human type tubercle bacilli. From the results obtained they concluded that there was "no doubt of the retarding effect on tuberculosis in the guinea pig, but it is also evident that this effect lasts only so long as treatment continues."

⁴ When measured by the Hopkins tube the suspension was found to contain 0.6 mg. of tubercle bacilli per milliliter.

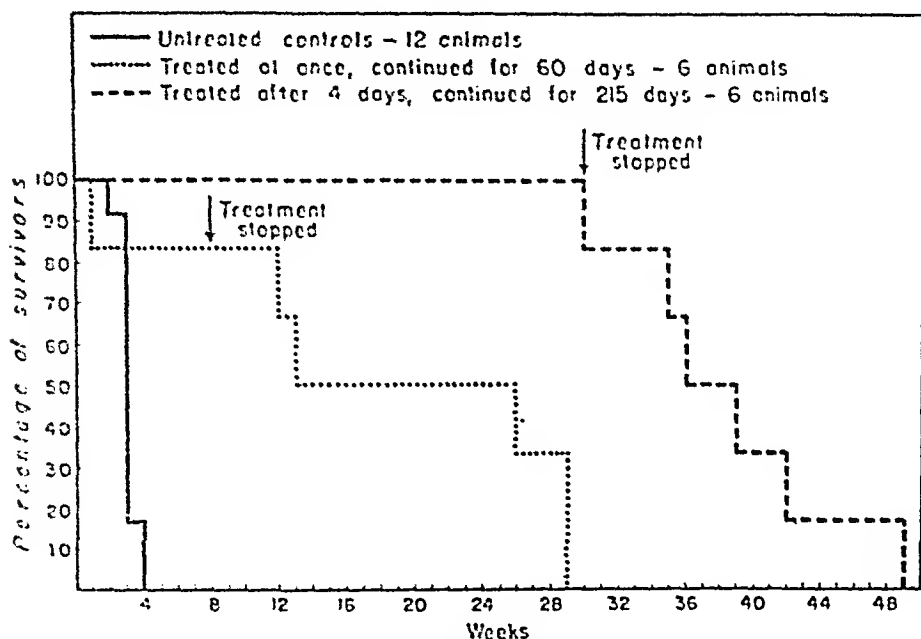
⁵ The streptomycin used in this study was supplied through the courtesy of Dr. D. F. Robertson, Merck & Co., Inc., Rahway, New Jersey.

RESULTS

Deaths: There was a striking difference in the survival times of the animals constituting the respective groups. These differences are shown in graph 1.

The first death among the untreated controls occurred on the eleventh day after infection. The last animal in this group died twenty-seven days after being inoculated. The average survival time for the 12 animals in group 1 (untreated controls) was nineteen days.

In group 2 (in which treatment was started on the day of infection and continued for sixty consecutive days) one animal died after two days. The cause of death was not determined. This animal may be disregarded. No further deaths occurred in this group until the eighty-fourth day after infection, which



GRAPH 1. Relative survival times of three groups of animals.

was twenty-four days after treatment was discontinued. Another animal died on the eighty-sixth day. There were no additional deaths until the 179th day at which time the surviving animals in the group had received no treatment for approximately four months (119 days). The remaining 2 animals in this group died 193 days after being infected. They had received no streptomycin during the last 133 days of life.

In group 3, in which treatment was started on the fourth day after infection and continued for 215 days, the first death occurred 210 days after the animal had been infected. The days of survival after infection for the remaining 5 guinea pigs in group 3 were 245, 248, 271, 294 and 341, respectively. The duration of survival after treatment was stopped for these 5 animals varied from one month to approximately four months.

The data obtained from this phase of the study demonstrated strikingly the ability of streptomycin to prolong the life of animals infected with a potentially rapidly lethal dose of tubercle bacilli. This fact becomes impressively evident when it is recalled that, of the 12 animals that were not treated, all died during the first twenty-seven days after inoculation. Of the 11 animals that constituted

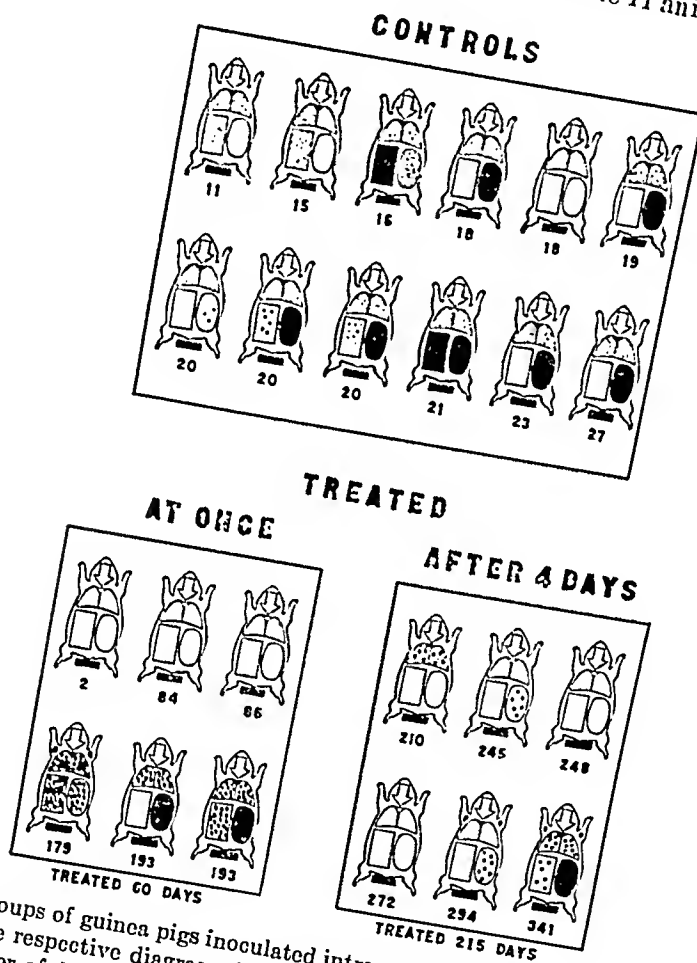


FIG. 1. Three groups of guinea pigs inoculated intravenously with tubercle bacilli. The black bar under the respective diagrams indicates that the animal died and the numerals represent the number of days the respective animals lived after inoculation with tubercle bacilli.

the two groups that were treated it is of interest to note that 8 lived six months or longer.

Pathological changes: The amount of tuberculosis noted at the time of necropsy and recorded schematically in the three groups of guinea pigs is shown in figure 1. The rapidity with which the disease developed in the untreated controls is strikingly evident. As might be expected, in all instances severe miliary tuberculosis developed in the lungs and in most of the animals the spleen was similarly in-

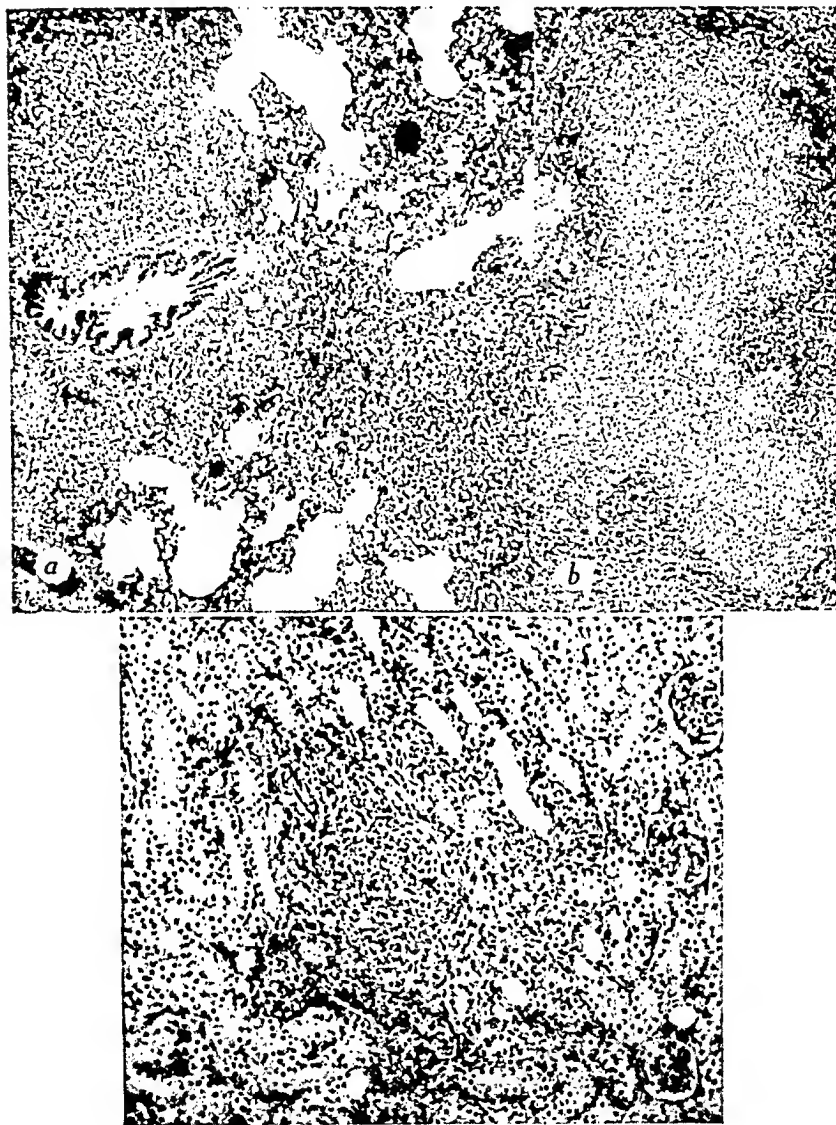
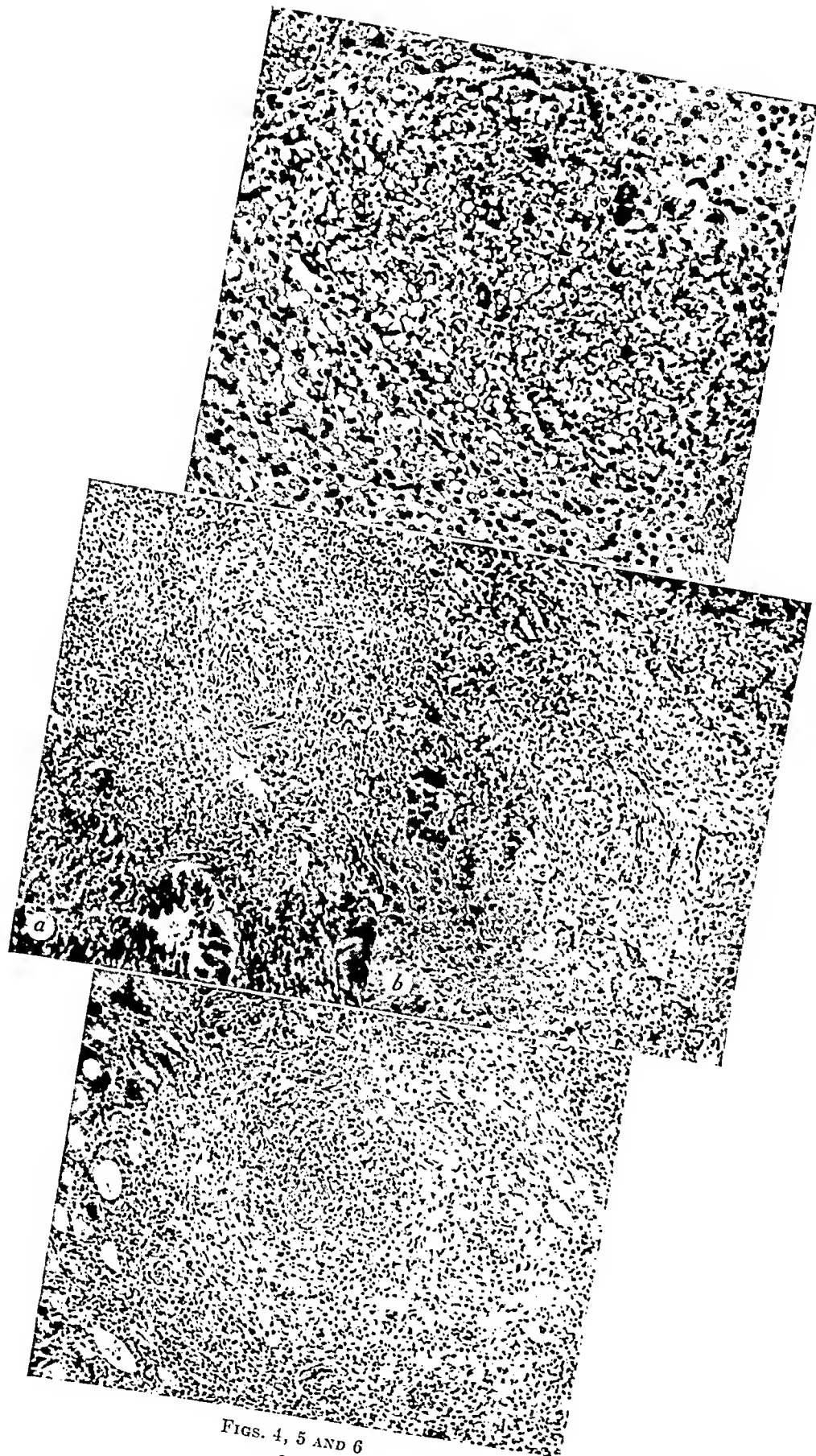


FIG. 2. (upper) *a*) Lung of untreated guinea pig. Animal died fifteen days after intravenous inoculation of tubercle bacilli. Severe hematogenous tuberculous pneumonitis ($\times 53$). *b*) Spleen of untreated guinea pig. Animal died twenty days after intravenous inoculation with tubercle bacilli. Progressive tuberculosis involving splenic nodule. The splenic pulp spaces were also extensively involved ($\times 53$).

FIG. 3. (lower) Kidney of untreated guinea pig. Death occurred twenty days after intravenous inoculation of tubercle bacilli. Small tuberculous focus in the cortical region ($\times 90$).

involved. Grossly the liver showed less disease than the spleen and the lungs did.

Microscopically the disease in the untreated controls was widely disseminated and characteristic of a highly virulent, hematogenous infection. In 2 of the ani-



FIGS. 4, 5 AND 6

imals miliary foci were found in the kidneys but in no instance were tuberculous changes found in tissues of the central nervous system.

In the lungs the disease became more diffuse as the duration of life was extended. As a consequence in some of the animals the lungs showed wide-spread tuberculous pneumonia with numerous small to large areas of necrosis (figure 2a). In most instances the disease in the liver maintained its discrete, nodular form with some evidence of peripheral expansion. The disease in the spleen was severe and extensive. In many instances the normal histological landmarks were obliterated (figure 2b). The lesions of tuberculosis found in the kidneys were of small dimensions and consequently of minor destructiveness. In all instances the lesions in the kidneys were situated in the cortex (figure 3).

The total appearance of the morbid changes in the group of untreated controls was that of a rapidly progressive, destructive, fulminating tuberculosis. The severity and extent of the disease were clearly apparent from the microscopic studies. The character and extent of the disease left no doubt about the vulnerability of the guinea pig to large doses of virulent tubercle bacilli of the human type introduced directly into the blood-stream. When these conditions obtain, death is sure and soon.

As may be noted in figure 1, 2 animals in group 2 (treated for sixty days) had no gross lesions of tuberculosis when death occurred eighty-four and eighty-six days, respectively, after inoculation. Microscopically no tuberculosis was observed in the lungs, liver or spleen of one of these animals. In the other guinea pig the lungs and spleen were not involved although a few regressive foci were present in the liver (figure 4). Numerous foci of active tuberculosis were found in the tracheobronchial lymph nodes of both animals.

The disease in the 3 remaining animals in group 2 was of varied character.⁶ The spleen of each animal was extensively involved and the disease was active and progressive. The same was true of the lungs of 2 of the animals, while in the lungs of the third areas of fibrosis indicative of a healing process were noted (figure 5a). In none of the 3 guinea pigs were lesions of active tuberculosis found in the liver. Instead, residual disease consisted of irregular regions of cirrhotic scarring with little if any histological resemblance to tuberculosis (figure 5b).

⁶ As mentioned previously, the sixth animal in group 2 died two days after inoculation and is not included in the study.

FIG. 4. (upper) Liver of guinea pig treated for sixty days with streptomycin; group 2. Animal died twenty-four days after treatment had been discontinued. No parenchymal lesions observed at necropsy. Nonspecific regressive lesion composed largely of "foam cells" ($\times 170$).

FIG. 5. (centre) a) Lung of guinea pig in group 2; treated for sixty days with streptomycin; died 133 days after treatment had been stopped. Area of fibrosis ($\times 90$). b) Liver of guinea pig in group 2; treated for sixty days with streptomycin; died 119 days after treatment had been stopped. One of several areas of cirrhotic changes ($\times 90$).

FIG. 6. (lower) Kidney of guinea pig in group 2; treated with streptomycin for sixty days; died 119 days after treatment had been discontinued. Healing tuberculous nodule with remnants of glomerulus ($\times 90$).



Tuberculosis of the kidneys was found in one of the guinea pigs in group 2. The animal died on the 179th day after infection and had received no treatment for the last 119 days of life. The lesions in the kidneys consisted of a few cortical foci with dense fibrotic encapsulation of small central areas of necrosis (figure 6). In this animal and in one other there was also observed severe active tuberculosis of the testicles. In each of the last 3 animals to die in group 2, active myocardial tuberculosis was found. These lesions were characterized by central areas of necrosis and peripheral fibrosis or healing. As was true in the untreated controls, in no instance were tuberculous lesions found in the tissues of the central nervous system.

In group 3, in which treatment was started four days after infection and continued for 215 days, impressive morphological evidence of suppression of the disease was present in 4 of the 6 animals. The spleens of 2 of these 4 animals contained only fibrotic foci with no recognizable signs of activity (figure 7*a*). In 2 other animals the spleens appeared to be essentially normal. In the spleens of the remaining 2 animals in group 3 moderate to severe tuberculosis was present. These animals died 294 and 341 days, respectively, after being inoculated (figure 7*b*).

Very little tuberculosis was found in the livers of the animals in group 3. In 2, signs of the disease were absent. In each of the other 4 animals the liver contained a few retrogressive foci, some of which were definitely sclerotic. In fact, the healing tendencies of many of the foci in the liver were sufficiently advanced to appear as nonspecific granulomatous reactions (figures 8*a* and *b*).

Microscopic study of the lungs of the animals in group 3 revealed a few apparently nonactive discrete tuberculous nodules in 3 animals, no lesions in the lungs of one and moderate to severe tuberculosis in 2. In one of the latter a bone-like structure of questionable significance occurred. Whether or not this represented a residual lesion of previously active tuberculosis could not be determined.

The kidneys of only 4 of the 6 animals in group 3 were available for histological study. In 2 no lesions were found, while in the remaining 2 the kidneys showed fibrosis and other evidence of healing tendencies (figure 9).

FIG. 7. (upper) *a*) Spleen of guinea pig, group 3. Treated with streptomycin for 206 days; died 210 days after inoculation. Spleen had no gross lesions; microscopically this organ contained several fibrotic or healing tubercles ($\times 90$). *b*) Spleen of guinea pig, group 3. Animal died 294 days after inoculation and seventy-nine days after treatment with streptomycin had been discontinued. The spleen contained areas of dense fibrosis with much obliteration of normal structure. Other areas of this spleen showed changes suggestive of active tuberculosis ($\times 90$).

FIG. 8. (centre) *a*) Liver of guinea pig, group 3. Treated with streptomycin for 215 days; died after being off treatment for 126 days. Sclerotic nodule suggestive of healed tuberculosis ($\times 90$). *b*) Liver of guinea pig, group 3. Treated with streptomycin 215 days; died after being off treatment for seventy-nine days. Sclerosing nodule with slight evidence of activity ($\times 90$).

FIG. 9. (lower) Kidney from same guinea pig shown in figure 8*b*. Area of tuberculosis showing healing tendencies with early calcification ($\times 90$).

In only one animal of this group—the last of the group to die—were the testicles involved. In this animal both testicles and epididymis were severely affected. In no instance were lesions of tuberculosis found in the brain or spinal cord.

At the time of necropsy gross examination of the hearts of the animals in group 3 failed to reveal lesions suggestive of tuberculosis. Unfortunately, owing to inadvertence none of the hearts in this group were examined microscopically.

The study of the histopathological characteristics of the tissues obtained from the guinea pigs in group 3 disclosed that the prolongation of treatment had resulted in a more complete arrest of the disease than was true in the animals that were treated for only sixty days. This was clear from the abundant morphological evidence of healing of residual lesions in the animals in group 3. The tendency of the lesions to undergo fibrosis and the many instances in which signs of activity were missing in the organs of predilection indicate definitely that anatomically tuberculosis in guinea pigs may be profoundly altered in a favorable manner by a therapeutic agent of adequate potency.⁷

It will be recalled that each of the 24 animals in this study received the infective inoculum into a superficial vein of the penis. No lesions of tuberculosis were found either grossly or microscopically in the tissues of the penis.

Residual infections and resistance to streptomycin: At the time of necropsy a portion of the spleen from each of the animals treated with streptomycin was utilized to prepare cultures for tubercle bacilli. Tubercle bacilli were eventually obtained from 7 of the 11 treated animals included in this report. The 4 instances in which the cultural attempts gave negative results represented splenic tissues in which comparable portions of the same organs failed to reveal lesions of tuberculosis, grossly or microscopically.⁸ In 2 instances in which no lesions of tuberculosis were found in that portion of the spleen examined, cultures of tubercle bacilli were obtained.

The cultures obtained from the spleens previously mentioned were subjected to *in vitro* tests to determine their relative sensitivity or resistance to streptomycin.⁹ The results of this phase of the study are shown in table 1.

It may be noted that cultures resistant to streptomycin were obtained only from those animals treated for prolonged periods. It is of interest that resistant cultures of tubercle bacilli were obtained from animals that had been off treatment for many weeks. In 2 instances resistant cultures were obtained from guinea pigs in which there was no microscopic evidence of active tuberculosis.

⁷ At the time of necropsy several of the animals in this experiment did not present sufficient tuberculosis to account for death. A subsequent study by our associates, Dr. L. A. Weed and Dr. F. R. Heilman, of the cause of death, prematurely, of guinea pigs dying in our laboratory has revealed the virus of lymphocytic choriomeningitis. Without definite proof that this was the cause of death in the animals dying prematurely in this experiment, the presence of this viral disease, among our animals, suggests a possible explanation.

⁸ Two specimens were from animals in group 2 and one was from an animal in group 3.

⁹ The method used was that described previously (4).

While these data are of some interest, they are inadequate to justify conclusions as to the significance of the presence of streptomycin-resistant tubercle bacilli in animals that have shown a favorable response to earlier treatment with streptomycin. This problem should be subjected to further and more extensive investigation. The isolation of streptomycin-resistant tubercle bacilli from guinea pigs treated with this drug is of some interest, since this is the first time we have succeeded in demonstrating that streptomycin-resistant tubercle bacilli may be isolated from treated guinea pigs. Many previous attempts to demonstrate this phenomenon in guinea pigs treated with streptomycin have been futile. Perhaps the previous failures were due to the fact that the animals had not been treated for a sufficiently long period.

The results demonstrate that in the tuberculous guinea pig, as in the tuberculous human being, prolonged treatment with streptomycin may eventually

TABLE 1

Growth inhibitory action in vitro of streptomycin against cultures of tubercle bacilli obtained from spleens of treated animals

CULTURE	DURATION OF TREATMENT IN DAYS	DAYS WITHOUT TREATMENT BEFORE DEATH	MICROGRAMS OF STREPTOMYCIN PER ML. OF MEDIUM NECESSARY TO INHIBIT GROWTH	ACTIVE LESIONS*
1	60	133	0.31	+
2	60	133	0.31	+
3	206	None	>2,000	-
4	215	30	>2,000	+
5	215	56	>2,000	-
6	215	79	>3,000	+
7	215	126	>3,000	+

* "Active lesions" refers to the results of the microscopic study of liver, spleen, lungs or other tissues from guinea pigs from which the respective cultures were obtained.

result in a population of tubercle bacilli that have a profound resistance *in vitro* to streptomycin.

SUPPLEMENTARY EXPERIMENTS

After the foregoing experiment had been under way for approximately six months, a second study of essentially the same character was started. The objective of the second experiment was to determine whether treatment with streptomycin would be effective therapeutically if the beginning of treatment was delayed for a longer period than was true in the first experiment.

The second study differed from the first in a few details. The infecting organism was one obtained a short time previously from a tuberculous patient. In the first experiment tubercle bacilli of strain H37Rv had been used. A total of 29 male guinea pigs was used and each animal was inoculated intravenously with 0.5 mg. moist weight of tubercle bacilli. Treatment of 14 animals with streptomycin was started when the first infected animal died. This occurred on the eleventh day after infection. The dose of strep-

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tomycin per animal was 3 mg. given subcutaneously twice daily (total dose per twenty-four hours: 6 mg.). Treatment was continued until all of the treated animals had died.

Results: The 15 animals in the group of untreated controls were all dead by the twenty-third day. All had severe generalized tuberculosis which was the apparent cause of death. Among the treated animals 6 died on the fourteenth day after infection (three days of treatment). Three additional ones died between the fifteenth and the thirtieth day (four to nineteen days of treatment) and the remaining 5 died between the thirty-first and the fifty-fourth day (twenty to forty-three days of treatment). The data show that at the time when the untreated controls had all died, one-half or 7 of the animals treated with streptomycin had also succumbed.

Except for the prolongation of life of one-half of the animals that were treated there was no evidence of the therapeutic value of streptomycin in this study. The treated animals, like the untreated controls, died of wide-spread tuberculosis.

The results of this supplementary experiment indicate, as did the first experiment, that tuberculosis established in the untreated guinea pig by the intravenous inoculation of a large dose of virulent tubercle bacilli is an exceedingly formidable, intractable disease. The results also suggest that under the conditions imposed in the supplementary study a satisfactory deterrent effect on the progress of the infection cannot be obtained when treatment with streptomycin is delayed until the first of the untreated animals dies of tuberculosis. After the disease has been permitted to progress uninhibited for this period, the infective process appears to be irreversible in so far as the use of streptomycin is concerned. Contrary to this impression are the results observed in the first experiment. When treatment was started at once or delayed for only four days after the animals were inoculated there was a definite and convincing suppression of the infection. It is obvious that, when the disease in the guinea pig reaches sufficiently formidable proportions, the potential therapeutic results of streptomycin are markedly limited.

COMMENT

The limited studies recounted in this report have provided certain information regarding the potency and limitations of streptomycin in combating inoculation tuberculosis in the guinea pig.

The magnitude and severity of tuberculous infections produced in guinea pigs by the intravenous inoculation of virulent tubercle bacilli of the human type provide a form of experimental disease that offers profound difficulties for any known or hypothetical chemotherapeutic agent.¹⁰ Intrinsically the tubercle bacillus and the diseases it produces have constituted an exceedingly stubborn problem for the chemotherapist. Even under the most favorable experimental

¹⁰ Youmans and McCarter (5) have shown the therapeutic potentialities of streptomycin in the treatment of mice inoculated intravenously with human type tubercle bacilli. Martin (6) has also used the same method of procedure in studying the therapeutic effectiveness of various substances against tuberculous infections.

mental conditions specific substances that have exerted a favorable modification of the expected course of the disease have been few indeed.

Therefore, any drug capable of exerting even a limited deterrent effect on a tuberculous infection of such lethal proportions as that which follows intravenous inoculation has impressive therapeutic possibilities. Furthermore, the results obtained in the first of the two experiments described in this report provide additional evidence of the vulnerability of tuberculous infections to specific therapeutic substances. It is true that the results were not all that one might hope to obtain from the ideal tuberculo-chemotherapeutic substance; a more effective drug is greatly to be desired. Nevertheless, even though the shortcomings of streptomycin are fully recognized, the fact remains that this substance is capable of modifying favorably, and often dramatically, the development of tuberculosis under highly unfavorable conditions.

The tissues obtained from the treated animals in the first study provided an opportunity to learn more concerning the histopathological characteristics of tuberculosis after treatment with streptomycin. As was previously described, many of the residual lesions had impressive signs of a reactive process that was no longer progressive. Many lesions appeared definitely quiescent, with abundant signs of fibroblastic transformation. Many instances of sclerotic changes were noted and lesions persisted in which the identifying features of tuberculosis were no longer detectable. Similar changes have been described previously in tuberculous guinea pigs treated with streptomycin and in human beings treated with this drug (7). It appears therefore that, even in the highly susceptible guinea pig, tuberculosis may, under the influence of a potent therapeutic agent, change from an advancing destructive disease to one of less menacing proportions in which the healing process is active.

The activation or acceleration of the healing propensities of tuberculous lesions after or during treatment with a drug such as streptomycin has an important connotation in clinical tuberculosis. Even though the disease in patients treated with streptomycin may be only suppressed during the actual period of treatment, there are reasons for believing that the beneficent effects of the treatment continue in most cases long after the administration of the drug has been stopped. This is true in some instances in which at the end of the treatment period the great majority of tubercle bacilli isolated from the patient have a profound *in vitro* resistance to streptomycin. This suggests that, as a result of the deterrent action of streptomycin on sensitive tubercle bacilli during the earlier phase of the treatment period, the healing process has been activated and keeps pace and eventually outdistances the ability of the infection to progress. It would appear, therefore, that a satisfactory therapeutic response of tuberculosis to streptomycin is dependent on at least two factors: first, the specific antibacterial action of the drug on tubercle bacilli sensitive to the action of streptomycin and, second, the intrinsic potential of the infected host to mobilize effectively the intangible factors of resistance manifested in the healing process.

The search for drugs which may be superior to streptomycin will surely con-

tinue for a long time. It is suggested that before such drugs are declared to be superior to streptomycin they should be submitted to rigid tests such as are described in the present communication.

For the first time in our experience the supplementary experiment described earlier in this paper has produced an experimental infection in guinea pigs so severe as to be beyond the capacity of streptomycin to control. Thus we have determined what might be regarded as the "end point" of therapeutic efficacy of this substance in treatment of experimental tuberculosis. Should other substances be found which can exceed streptomycin in therapeutic performance under these severe conditions, they should immediately become of great interest.

We should like to emphasize here as in previous publications that the histological examination of organs of experimental animals involved in studies on tuberculosis supplies significant information which cannot be supplied by gross examination alone. Without such microscopic examination it is possible to overestimate greatly the therapeutic value of a drug in studies on experimental animals.

Finally, it is regrettable that the observations recorded for the first experiment are based on relatively few animals. The results would obviously be of greater significance if an experiment of larger proportions had been done. However, the data obtained do suggest that the pathogenesis of experimental tuberculosis induced intravenously may be greatly modified by streptomycin, provided that treatment is instituted during the earlier phases of the infection. The clinical implications of the results are that, in cases of disseminated, hematogenous tuberculosis, treatment should be started as early as possible if the maximal therapeutic effect is to be accomplished.

SUMMARY

Experiments are described in which guinea pigs were inoculated intravenously with large doses of virulent human type tubercle bacilli (H37Rv) and treated with streptomycin. In the first experiment one group of animals was treated, beginning at the time of inoculation and continuing for a period of sixty days. A second group in the same experiment was treated starting four days after inoculation and continuing for 215 days. All untreated controls died within twenty-seven days, but the duration of life of the animals in the two groups that received streptomycin was markedly extended. All treated animals eventually died, the last 341 days after inoculation. Many had extensive lesions of tuberculosis. Morphologically, however, there was impressive evidence that the residual lesions were in many instances no longer progressive but instead were quiescent, healed or healing.

The possible significance of these observations is discussed from a theoretical and from a clinical point of view.

A second or supplementary experiment is briefly described. The animals were also inoculated intravenously but treatment with streptomycin was delayed until the first of the untreated control group had died. Death of this animal occurred on the eleventh day after infection. The results of treatment

in this experiment were definitely inferior to those observed when treatment was started earlier.

SUMARIO

La Estreptomicina en la Tuberculosis Experimental

En los experimentos descritos se inoculó intravenosamente en cobayos 1.0 mg. de bacilos tuberculosos de tipo humano (H37Rv), tratándoseles después con estreptomicina. En el primer experimento un grupo de animales fué tratado desde el momento de la inoculación por espacio de sesenta días. En el mismo experimento otro grupo fué tratado desde cuatro días después de la inoculación por espacio de 215 días. Todos los testigos no tratados murieron en término de vintisiete días, pero en los dos grupos que recibieron estreptomicina la duración de la vida se alargó decididamente, aunque todos los animales por fin murieron, el último a los 341 días de la inoculación. Muchos mostraron extensas lesiones tuberculosas. Sin embargo morfológicamente, había pruebas imponentes de que las lesiones residuales en muchos casos habían cesado de ser evolutivas, convirtiéndose en quiescentes, cicatrizadas o en vías de cicatrización.

El posible significado de estas observaciones es discutido desde los puntos de vista teórico y clínico.

Describe sucintamente otro experimento complementario, en el que también se inoculó a los animales intravenosamente, pero demorando la estreptomicinoterapia hasta después de morir el primero de los animales testigos, lo cual sucedió a los once días de la infección. En este segundo experimento los resultados del tratamiento fueron netamente inferiores a los observados cuando el tratamiento fué iniciado antes.

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DERIVATIVES OF DIAMINODIPHENYLSULFONE AND HETEROCYCLIC SULFONES IN EXPERIMENTAL TUBERCULOSIS^{1,2}

B. L. FREEDLANDER AND F. A. FRENCH

Since the discovery that diaminodiphenylsulfone was effective in experimental tuberculosis, many of its derivatives and some closely related compounds have been made with the hope of finding a superior therapeutic agent. (Hereafter "diaminodiphenylsulfone" will be referred to as "DDS.") In addition to the well known DDS derivatives promin and diasone and the DDS isostere promizole, more than a hundred other derivatives have been prepared by many workers. To date, these efforts for the most part have been disappointing. DDS has the same or a greater order of effectiveness than any of its derivatives, both *in vitro* and *in vivo*, although its toxicity is higher than that of most of its derivatives. Recently, Youmans and Doub (1) have reported relatively high effectiveness for several nuclear substituted DDS derivatives and several isosteric unsymmetrical sulfones. They found that mono-2 or 3-methyl or chloro-DDS were approximately half as active as the parent compound and that the insertion of a 2 aldoxime group doubled the activity of DDS. Most nuclear substitutions caused a very considerable drop in activity. Among the sulfones isosteric with DDS some involving pyridine and thiazole nuclei were found to be fairly effective. A number of such derivatives synthesized by Bambas (2) were also found to be effective against streptococcus infections.

In the following experiments several new nuclear substituted derivatives of DDS and a new type of heterocyclic analogue have been evaluated *in vitro* and in experimental tuberculosis in guinea pigs. The DDS derivatives studied were the 2-chloro; 2,2'-dichloro; 3,5-dichloro; 3-methoxy and the N substituted derivative, 4-(p)dimethylaminobenzalamino,4'-aminodiphenylsulfone. These compounds were studied *in vivo* and *in vitro*. 4-Aminophenyl,6'-amino,2'-benzothiazoyl sulfone and 4-aminophenyl-6'-nitro,2'-benzothiazoyl sulfone were only tested *in vitro*, while 4-acetylaminophenyl,6'-nitro,2'-benzothiazoyl sulfone and 4-acetylaminophenyl,6'-amino,2'-benzothiazoylsulfone were tested *in vivo* and *in vitro*. The (p)dimethylaminobenzal derivative of DDS is of interest because the authors (3) have reported high therapeutic activity and low toxicity for the closely related compound 4-benzalamino,4'-aminodiphenylsulfone.

Although only two of the compounds evaluated in these experiments showed a significant therapeutic effect, this report is offered as an addition to the total accrued knowledge of the chemotherapy of sulfones. So that these experimental results could be related to those of other investigators, 4,4'-diaminodiphenylsulfone was tested simultaneously with other compounds as a control and reference drug.

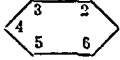
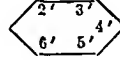
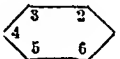
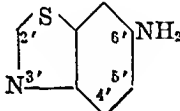
¹ From The Harold Brunn Research Institute, Mt. Zion Hospital, San Francisco, California.

² The present report is part of a coöperative investigation on tuberculosis, and has been supported by funds provided by the Committee on Medical Research of the National Tuberculosis Association, the California Tuberculosis Association, the San Francisco Tuberculosis Association, the Columbia Foundation of San Francisco.

IN VITRO EXPERIMENTS

The *in vitro* bacteriostatic studies were performed on the avirulent strain of human tubercle bacilli, No. 607 of the American Type Culture Collection, using a modified Sauton's synthetic medium, at a pH of 7.5. The chemicals were dissolved in propylene glycol to make solutions equivalent, on a molar basis, to 0.5 per cent DDS. Subsequent dilutions were made directly into the media. Each tube was inoculated with a saline

TABLE 1
Tuberculostatic action

NUM- BER	COMPOUND	CHEMICAL FORMULA	BACTER- IOSTATIC CONCENT- RATION
			mg. %
1.	4,4'-Diaminodiphenylsulfone	H_2N  SO_2  NH_2	0.5
2.	2-Chloro,4,4'-diaminodiphenylsulfone		0.5
3.	2,2'-Dichloro,4,4'-diaminodiphenylsulfone		1.0
4.	3,5-Dichloro,4,4'-diaminodiphenylsulfone		1.0
5.	3-Methoxy,4,4'-diaminodiphenylsulfone		0.25
6.	4-(p)Dimethylaminobenzal-amino,4'-aminodiphenylsulfone		2.5
7.	4-Aminophenyl,6'-amino,2'-benzothiazoyl sulfone	H_2N  SO_2  NH_2	10.0
8.	4-Aminophenyl,6'-nitro,2'-benzothiazoyl sulfone		2.5
9.	4-Acetylaminophenyl,6'-amino,2'-benzothiazoyl sulfone		10.0
10.	4-Acetylaminophenyl,6'-nitro,2'-benzothiazoyl sulfone		>10.0

Note: The above compounds were prepared in this laboratory under the supervision of Dr. F. A. French.

suspension containing 1 mg. of a fresh culture of tubercle bacilli. The cultures were read at the end of five days. The highest bacteriostatic dilution was taken as that dilution in which there was no or very slight growth.

ANIMAL EXPERIMENTS

Nine to 12 guinea pigs, averaging 350 to 400 g. in weight, were used to evaluate each compound. The animals were inoculated in the left groin with 0.01 mg. of H37Rv tubercle bacilli. Therapy was started on the same day. The drugs were mixed with

finely ground rabbit pellets. The food was supplemented with fresh vegetables daily. The dosage of the drugs was usually increased gradually for the first three weeks of the experiment. The experiments were terminated at the end of six weeks. Tuberculosis was evaluated numerically by the method of Sweany, Sher and Kloeck (4), in which the maximum gross involvements of the organs were given the following numerical ratings; lymph nodes 8, spleen 24, liver 28 and lungs 40. The animals were weighed at weekly intervals. Hemoglobin determinations were made at the end of the experiments.

RESULTS

The *in vitro* bacteriostatic results are recorded in table 1. All of the nuclear substituted derivatives of DDS showed approximately the same order of bacteriostatic action as DDS (within ± 1 dilution). The tuberculostatic action of

TABLE 2
Summary of therapeutic efficacy in tuberculous animals

GROUP	COMPOUND	DAILY DOSAGE	AVERAGE TUBERCULOSIS RATING	PATHOLOGICAL RATIO	AVGE. WEIGHT GAIN	HGB.
				CONTROLS TREATED		
A	4,4'-Diaminodiphenylsulfone	mg.	27.7	1.66	154	9.8
	3-Methoxy,4,4'-diaminodiphenylsulfone*	50-100	39.9	1.15	192	11.6
	2,2'-Dichloro,4,4'-diaminodiphenylsulfone†	70-100				
	3,5-Dichloro,4,4'-diaminodiphenylsulfone	50-100	33.6	1.37	236	11.6
	4-Acetylaminophenyl,6'-nitro,2'-benzothiazoyl sulfone	50-100	30.9	1.48	146	9.5
	4-Acetylaminophenyl,6'-amino,2'-benzothiazoyl sulfone	75-150	40.7	1.13	170	11.3
	Controls	75-150	39.2	1.17	97	11.2
			45.9		188	12.3
B	4-(p)Dimethylaminobenzalamino,4'-aminodiphenylsulfone	100	16.3	2.35	133	10.8
	Controls		38.4		118	12.
C	2-Chloro,4,4'-diaminodiphenylsulfone	50-75	20.5	2.21	148	10.5
	4-(p)Dimethylaminobenzalamino,4'-aminodiphenylsulfone	300.	12.6	3.60	53	9.7
	Controls		45.4		106	11.4

* Therapy discontinued after twenty-five days due to insufficient amount of drug.
† Therapy deferred for five days after infection.

the four benzothiazoyl sulfones was of a much lower magnitude. The DDS derivatives were all antagonized by para-aminobenzoic acid, but the benzothiazoyl sulfones were not. The *in vivo* results are summarized in table 2. 2,2'-Dichloro and 3,5-dichloro DDS showed marginal activity inferior to DDS. 2-Chloro DDS is as effective or more effective than the parent compound.

3-Methoxy DDS showed no significant therapeutic effect but this may have been due to cessation of drug administration after three weeks. 4-(p)Dimethylamino-benzalamino, 4'-aminodiphenylsulfone was tested at two dosage levels, 100 mg. and 300 mg. daily. At equivalent molar dosage levels this compound is considerably more effective, as shown by the disease ratios, than DDS. DDS and most of its derivatives produced enlarged and cyanotic spleens but this effect did not occur with 3-methoxy DDS or 2,2'-dichloro DDS. Animals receiving these two compounds had better hemoglobin readings than are usually found with DDS and its derivatives. The benzothiazoyl sulfones showed no significant therapeutic effect. The spleens of animals receiving them were not cyanotic and no gross enlargement of their thyroid glands was noted.

DISCUSSION

In previous work the authors (3) found that 4-acetyl-amino, 4'-nitrodiphenyl-sulfone was active *in vivo*, presumably because of *in vivo* conversion to DDS. In the present experiments the two acetylated benzothiazoyl sulfones were tested *in vivo* because it was felt that they might be reduced and deacetylated *in vivo* to reveal any potential effectiveness for this type of sulfone. 4-Aminophenyl,6'-amino,2'-benzothiazoyl sulfone (compound No. 7) and 4-aminophenyl-6'-nitro,2'-benzothiazoyl sulfone (No. 8) were not evaluated *in vivo* because of preparative difficulties. The benzothiazoyl sulfones were tested also to see if the effect on the thyroid of drugs like promizole could be avoided by this structural modification. Promizole has a thioureoid structure and the 2-benzothiazoyl sulfones do not. This structure-activity relation was borne out in the experiments. A further factor of interest in connection with the benzothiazoyl sulfones is that they are not antagonized by para-aminobenzoic acid. This suggests the possibility of tuberculostatic activity intrinsic in the benzothiazole portion of the molecule and quite independent of the sulfa type structure.

In reference to the DDS derivatives it is apparent that the (p)dimethylamino-benzal derivative of DDS is at least equivalent to promin and diasone. The 300 mg. dosage level was the maximum tolerated level for this drug. Of the nuclear substitution derivatives of DDS, alkoxy derivatives may offer some promise for improvement and the results shown for 3-methoxy DDS in this paper should not be considered conclusive because of the conditions of the test.

Although at one time doubt was expressed regarding the merit of strain 607 as a screening test organism, its usefulness is now well recognized. Such *in vitro* data combined with occasional cross checks using strain H37Rv and general chemical considerations are useful in eliminating compounds having a low probability of *in vivo* effectiveness. Recent unpublished data indicate that this generalization concerning the value of strain 607 as a screening organism, while apparently valid for drugs of the sulfa type, which have broad bacteriostatic spectra, may not be valid for drugs of a high order of specificity. Compounds which are inactive *in vitro* but are constituted so that they might be converted to active forms *in vivo* should be tested further.

In conclusion, it is apparent that many structural variants in the sulfone group

have not been touched. The possibilities are greater in variety than in the well explored sulfonamide group and the distinct advantage of non-ionic character favoring cell penetration resides with the sulfones in contrast to some other sulfonamide type drugs. It is to be hoped that further studies will be made in this group of structures but not at the expense of ignoring many unrelated fields of investigation.

SUMMARY

1. Chemotherapeutic studies were performed on a number of new derivatives of 4,4'-diaminodiphenylsulfone (DDS) and some related unsymmetrical heterocyclic sulfones.
2. Most nuclear substituted derivatives of DDS gave high *in vitro* bacteriostasis. These derivatives included: 3-methoxy; 2-chloro; 2,2'-dichloro; and 3,5-dichloro,4,4'-diaminodiphenylsulfone. The benzothiazoyl sulfones had low activities *in vitro* and *in vivo*.
3. 2-Chloro DDS was as effective as the parent compound *in vivo*. The therapeutic effect of the N(p)-dimethylaminobenzal derivative of DDS was superior to that of the parent compound.
4. The relation of this work to that of other investigators, and some correlative factors are discussed.

SUMARIO

Los Derivados de la Diaminodifenilsulfona y las Sulfonas Heterocíclicas en la Tuberculosis Experimental

1. Ejecutáronse estudios quimioterapéuticos con varios derivados nuevos de la 4,4'-diaminodifenilsulfona (DDS) y algunas sulfonas heterocíclicas asimétricas afines.
2. La mayor parte de los derivados sustitutos nucleares de DDS mostraron alta bacteriostasis *in vitro*. Estos derivados comprendieron: 3-metoxi, 2-cloro, 2,2'-dicloro, y 3,5-dicloro,4,4'-diaminodifenilsulfona. Las sulfonas benzotiazólicas mostraron menos actividad *in vitro* e *in vivo*.
3. El 2-cloro DDS se mostró tan eficaz como el compuesto radical *in vivo*. El efecto terapéutico del derivado N(p)-dimetilaminobenzálico de DDS fué superior al de la droga matriz.
4. Discútense además la relación de este estudio con los de otros investigadores, y algunos factores correlativos.

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XII PAN AMERICAN SANITARY CONFERENCE¹

Caracas, January 12 to 24, 1947

The XII Pan American Sanitary Conference, held in Caracas, Venezuela, January 12 to 24, 1947, included in its seven commissions a Commission on Tuberculosis (Epidemiology of Tuberculosis and New Developments in the Anti-Tuberculosis Campaign), which spent several days discussing public health measures in the control of this disease. The Conference was attended by official delegates from each of the 21 American republics and a number of invited delegates from public health organizations who were admitted to all sessions as observers and in some instances were officers of the constituent commissions.

The officers of the Commission on Tuberculosis were:

President—Dr. José Ignacio Baldó from Venezuela

Vice-President—Dr. Esmond R. Long, Delegate from the National Tuberculosis Association

Secretaries—Dr. J. Pablo Leyva from Colombia

Dr. César A. Bonetti Dupont from Argentina

At its final session the Commission on Tuberculosis adopted the following resolutions:

EPIDEMIOLOGIA DE LA TUBERCULOSIS Y NUEVAS ADQUISICIONES EN MATERIA DE LUCHA ANTITUBERCULOSA

1º. "Se recomienda la adopción del comando único en la Lucha Antituberculosa, dentro del Departamento Nacional, al cual competan los problemas de la Salud Pública, y bajo dirección técnica especializada, como el sistema que puede alcanzar mejores resultados, evitando incoordinación, duplicación y aplicación de criterios diferentes. La dirección técnica de este Comando deberá abarcar las actividades de la lucha, en los campos preventivo, curativo y de investigación, cualesquiera que sean los organismos que suministren fondos para la campaña."

2º. "Se recomienda el examen sistemático y periódico de colectividades aparentemente sanas por el método fluorofotográfico introducido por De Abreu, dando preferencia a aquellos grupos que los estudios epidemiológicos señalan como los más afectados, cuando los recursos no permitan su generalización.

Si este método se pone en práctica también con el objeto de investigación epidemiológica, deberán agregarse las reacciones tuberculínicas.

La intensificación de este método no debe hacerse a expensas de la labor del Dispensario, base actual de la lucha antituberculosa."

3º. "Teniendo en cuenta que ya existen trabajos que justifican la introducción de la vacuna B.C.G. dentro de la práctica de la administración sanitaria, se recomienda su uso sujeto a los principios clásicos establecidos en lo que toca a

¹ Summary of the report to the Board of Directors of the National Tuberculosis Association by Esmond R. Long, official delegate of the Association to the Conference.

su aplicación y a su valor, como un elemento que debe agregarse a las medidas de profilaxis de eficacia ya reconocida en la lucha antituberculosa, y sin que estas sufran ningún menoscabo."

Esta Comisión se ha limitado a recomendar las nuevas adquisiciones en materia de lucha antituberculosa, y por ello no ha considerado necesario insistir sobre las medidas reconocidas como fundamentales, que deben continuar incrementándose. Al mismo tiempo la Comisión aconseja estimular la investigación de nuevos métodos que mejoren la efectividad de los procedimientos recomendados, así como también la unificación de los mismos.

EPIDEMIOLOGY OF TUBERCULOSIS AND NEW DEVELOPMENTS IN THE
ANTITUBERCULOSIS CAMPAIGN

(English translation of the above Resolutions)

1. It is recommended by the Commission that a unified command be adopted in the antituberculosis campaign within each national Department of Public Health and placed under specialized technical direction. In the opinion of the Commission this is the system which can achieve the best results, avoiding incoördination and duplication, and the application of varying criteria pertaining under different systems. This technical direction should include all of the activities involved in tuberculosis control in the preventive, curative and investigative fields, regardless of the organization supplying funds for the campaign.

2. It is further recommended that systematic and periodic examinations be made of apparently healthy groups by the photofluorographic method introduced by de Abreu, with preference for those groups which epidemiological studies indicate are the most seriously affected, if resources do not permit the general application of the method. If the method is practised with the additional specific object of epidemiological study, it should be supplemented by the application of tuberculin tests. Intensification in the application of photofluorography should not be made at the expense of the normal tasks of the dispensary, for the latter is the actual basis of tuberculosis control.

3. Recognizing the fact that investigations are on record which justify the introduction of BCG vaccination within public health practice, it is recommended that this method be used, subject to established classical principles, as an element supplementing the means of prophylaxis already recognized in the antituberculosis campaign, provided that the latter procedures are not curtailed in consequence.

This Commission has limited its recommendations to new principles in the field of tuberculosis control and therefore it has not been considered necessary to reemphasize those methods which are already recognized as fundamental and which should continue to increase in their application. At the same time the Commission advises the stimulation of investigation of new methods which may increase the effectiveness of the procedures recommended, as well as unification of methods in application of these procedures. (Unofficial translation.)

The Conference at its general session discussed the future program of the Pan American Sanitary Bureau and reaffirmed its active interest in the World Health Organization. The following were elected as officers of the Pan American Sanitary Bureau:

Director Emeritus—Dr. Hugh S. Cumming

Director—Dr. Fred L. Soper

Assistant Director—Dr. John R. Murdock

Acting Secretary—Dr. O. Vargas

EDITORIAL

Primary Infection and Progressive Tuberculosis

In the pathogenesis of progressive tuberculosis, pulmonary or extrapulmonary, it has been a fairly general assumption that there are mainly two separate danger periods. The first, at the time directly following primary infection; the second, dependent upon a secondary exogenous infection or an endogenous exacerbation of lesions formed during the primary infection and separated by an unknown period of latency from primary infection. That primary infection with its direct consequences demands a certain toll of early mortality from disseminated tuberculosis, miliary or otherwise, from meningitis and from direct extension (in various modalities) from the primary complex—all this has been generally accepted and seems well substantiated by the early peak in tuberculosis mortality before the age of 5. The tuberculosis death rate of this age group is about three to four times greater than the lowest age-specific tuberculosis mortality in the group 5 to 14.

These data show that it is justified to stress the fact that primary infection in early childhood kills a certain percentage of its victims.

It is considerably more difficult to know whether this phenomenon that primary infection is fatal in a certain percentage is true only for early childhood or possibly throughout life and to what extent the *fatality* rate of primary tuberculosis is dependent on age. The urgency of these problems increases, of course, with the demonstrated decrease of childhood infection and the concurrent increase of primary infections in adults. Intimately connected with these questions are the further questions whether or not progressive pulmonary tuberculosis in adults is in a significant proportion of cases the direct consequence of primary infection, and, if so, whether or not primary progressive pulmonary tuberculosis in the adult can be differentiated clinically and roentgenologically from that disease which is caused by a secondary (endogenous or exogenous) infection in the presence of a more or less completely healed primary complex. Parenthetically it should be mentioned that many Scandinavian authors, who have contributed the most important studies to this problem, use the term "true" or "genuine" tuberculosis for what in our literature is commonly called "reinfection type" tuberculosis as contrasted with our "childhood type" tuberculosis.

In an impressive series of reports from the Scandinavian countries, and to a lesser extent from Switzerland and France, the relation between primary infection and progressive pulmonary tuberculosis in adults has been studied. In order to avoid confusion, it is probably best to consider here only the Scandinavian publications, the most significant of which are mentioned in the paper by Doctor Malmros in this issue of the REVIEW. Essentially similar reports, not mentioned by Doctor Malmros, have come from Denmark (see Johannes Holm in Public Health Reports, September 6, 1946, 61, 1298).

A complete unanimity of opinion does, of course, not exist between all these

Scandinavian investigators, but their points of agreement cover broad principles; and these, it seems to this writer, are not sufficiently known nor considered in the United States.

It is probably fair to state that most, if not all, contemporary Scandinavian authors agree that:

- (1) Primary infection occurs frequently after the age of 18 or 20.
- (2) Primary infection in adults is much more frequently accompanied by clinical symptoms, such as grip-like symptoms, fever and malaise, than is usually recognized in this country.
- (3) Primary infection in adults is frequently associated, particularly in young women, with erythema nodosum (in Sweden, erythema nodosum is reportable as tuberculosis), with exudative pleurisy and with parenchymal changes in the lung demonstrable by X-ray examination.
- (4) A large proportion of all cases of "genuine" tuberculosis is pathogenetically caused directly by primary infection. ("Most cases of tuberculosis of the lungs appear during the first or second year after the primary infection." (Frostad).)
- (5) While primary infection can be diagnosed with certainty only by tuberculin conversion, erythema nodosum and certain roentgenological changes should strongly suggest the diagnosis.

These Scandinavian investigations are based on many long-term studies, of which the recent publications by Frostad and by Hedvall are particularly impressive because of their extraordinarily careful and fully documented observations, with a large number of case reports with many roentgenographic reproductions of superb quality. Frostad presents essentially three groups of patients with progressive tuberculosis germane to the problem: (1) 100 patients in whom tuberculin conversion was observed before "genuine" tuberculosis developed; (2) 47 patients in whom conversion was not observed but erythema nodosum instead; (3) 41 patients who had a normal film within twelve months before the appearance of X-ray lesions. He concludes that "The destructive form of the pulmonary tuberculosis appears in most cases in close relation to the primary infection, generally less than 12 months afterwards." The main difference between Frostad and Hedvall concerns the roentgenological morphology of the first observable changes in the lung. Frostad has seen more frequently progression or reactivation of the primary focus itself, while Hedvall reaffirms his earlier observations with Malmros in 1938 (see *Am. Rev. Tuberc.*, 1939, 40, 118; 1940, 41, 549, 562, 770), now on a considerably larger material, that the so-called subprimary initial foci—usually distant from the primary parenchymal focus—are the most frequent first roentgenological signs of progressive pulmonary tuberculosis. But he agrees with Frostad and with many other Scandinavian authors "that phthisis arises to a great extent as a consequence of . . ." [primary tuberculosis in adults]. It seems possible that the direct progression or reactivation of the primary focus itself is more common in those cases in which the onset of phthisis follows tuberculin conversion within a few months.

The evidence presented in these two monographs and that by Holm and

also by Ustvedt appears to be convincing. There still remains the question of the relative frequency of progressive primary tuberculosis in adults. Holm quotes from a study of Sigrid Holm in Copenhagen: of 1,278 adults with tuberculin conversion, X-ray changes were observed in 181, or ca. 14 per cent, at the time of conversion and in an additional 225, or ca. 18 per cent, during follow-up examinations in a period of an average of 2.3 years; of all those, who showed X-ray changes, about 30 per cent developed "genuine tuberculosis."

It is, of course, impossible, in a brief note like this, to do justice to the studies mentioned in the foregoing paragraphs. That they contain a wealth of material which is carefully recorded and analyzed, has already been implied. They seem of such extraordinary significance that they should be read and studied by anyone who, in practice or in theory, is interested in the pathogenesis of tuberculosis.

One would like to know whether the Scandinavian observations are representative for conditions in the United States. For the time being, it is impossible to answer this question, simply because a totally insufficient number of studies concerned with this problem have, so far, been published in this country.

It is known that erythema nodosum in association with primary tuberculosis is extremely rare in this country. The shift of tuberculin conversion to higher age groups is equally well known as in Scandinavia; but, for all the rest, there is little evidence for or against the Scandinavian conclusions. According to the few available reports, a diagnostic differentiation between primary and secondary tuberculosis is impossible without tuberculin tests proving recent conversion; but impossibility of differentiating should not imply an absence of differences; and the most competent observers state that essentially the same anatomical differences exist in adults between primary and postprimary tuberculosis as in children. Finally, it would seem that clinical symptoms and objective signs of disease are observed, in the early period following conversion, considerably more frequently in Scandinavia than in the United States. It is still uncertain whether this is a difference in facts or rather in interpretation.

Since technological advances in radiography have made mass surveys feasible, most such surveys in the United States have been made without tuberculin tests, and few mass surveys have repeatedly examined the same persons. Serial tuberculin tests and repeated filming are, of course, two necessary methodological requirements for the elucidation of the relation between primary infection and progressive tuberculosis. From this point of view, mass surveys with over-enthusiastic emphasis on large numbers are not an unqualified blessing. It is good to find cases; but it is possibly even more important to learn how and why and where surveys should be done for the maximal benefit. It is hoped that the large study on nurses, now being carried on under the joint auspices of the National Tuberculosis Association and the U. S. Public Health Service, will provide material suitable for analysis from a pathogenetic point of view.

The Scandinavian studies reemphasize that pathogenesis of tuberculosis is a problem that can never be solved by the pathologist or the experimentalist, alone; but only by the careful integration of pathological, experimental, clinical-roentgenological and epidemiological methods. An illustrative example comes

to mind: When, some years ago, bacteriological studies on apparently healed primary foci established their sterility in an overwhelming majority, it was pointed out that such findings could hardly be accepted as proof for the assumption that progressive tuberculosis must be caused by exogenous reinfection, because (in view of studies, such as the Scandinavian) the main difference between persons who develop progressive disease and those who do not may possibly be the latter's ability to kill the bacilli of their primary infection, completely and in a reasonably short time; and that, therefore, necropsy findings in persons who never developed progressive tuberculosis may not be the proper material for studies on the pathogenesis of clinical tuberculosis.

A biological analogon to the present Scandinavian concept is infection with *Coccidioides immitis*; regardless of the clinical severity of the primary phase ("Valley fever"), the granulomatous phase with dissemination and a high fatality rate seems to develop within a few months of the first infection or not at all.

It should be obvious that pathogenetic knowledge is not of purely academic interest, but that it is unavoidably the foundation for all antituberculosis work and that it will determine the effectiveness of such work and the proper distribution of public health funds.

It is entirely possible that what is true in Scandinavia is not true in the United States. *Tuberculosis changes with time and place*. For this reason, every country (and possibly even smaller subdivisions) must investigate their local epidemiological conditions; none can accept, without proof, the findings in some other region.

As is so clearly stated in Doctor Malmros' paper, BCG vaccination is the logical consequence of the epidemiological situation in Scandinavia. If it should prove to be true for the United States that a large proportion of progressive tuberculosis in adults develops independently of a second exogenous infection, our present strategy of antituberculosis work would need fundamental reforms

MAX PINNER .

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THE AMERICAN REVIEW OF TUBERCULOSIS ABSTRACTS

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Hemopneumothorax.—The authors report a young naval officer who developed severe left chest pain on the day of admission to the hospital, rapidly went into profound shock and died on the same day. Clinical examination and chest aspiration established the diagnosis of hemopneumothorax. Autopsy revealed a massive left hemothorax, and a collapsed left lung with densely adherent apex. The apical adhesions were well vascularized and showed scattered hemorrhages. There was no evidence of active tuberculosis. Five days prior to admission, the patient had experienced pain in the left supraclavicular region after slinging a heavy bag over his left shoulder. This exertion might have torn the left apical adhesions resulting in slow bleeding. Thirteen other autopsied cases of spontaneous hemopneumothorax have been reported. All were males between the ages of 18 and 44 years. Unusual exertion or trauma did not seem to be etiological factors. In most cases, the first symptom of chest pain occurred when the patient was quiet. Abdominal pain and rigidity were common leading to laparotomy in one case. The right chest was more frequently involved. Pleural adhesions were found over the involved lung in 6. Torn adhesions were found in 5 cases and ruptured bullae in 4. In 3 cases, no lesions of the involved lung were found.—*Fatal Spontaneous Hemopneumothorax: Review of the Literature and Report of a Case, F. C. Helwig & E. C. H. Schmidl, Ann. Int. Med., April, 1947, 26: 608.*—(H. R. Noyer)

Hemothorax.—Only 145 cases of hemothorax without obvious cause have been described in the literature to date. Exclusive

of pulmonary tuberculosis and hemorrhagic effusions occurring as complications of collapse treatment, the number described is reduced to 44. Only 4 of the 44 were true hemothoraces unassociated with pneumothorax. Even these 4 cases suggested the possibility of hemopneumothorax in which air had been absorbed by the time the disease became obvious or failure to recognize the presence of air by roentgen examinations. It appears that most hemothoraces originate in rupture of vascular adhesions, either by a spontaneous pneumothorax or by extreme effort in which vascular adhesions are severed without pneumothorax. At necropsy spontaneous pneumothoraces have been related to ruptured blebs or cysts due to congenital or acquired pulmonary disease; the latter is most frequent on the basis of previous parenchymal tuberculosis. Bleeding is generally considered pleural rather than pulmonary. The clinical syndrome consists of sudden severe chest pain and dyspnea suggesting spontaneous pneumothorax followed by temporary improvement for hours or days with recurrence of pain and dyspnea and the appearance of signs of hemorrhage. Three case reports are presented, the first of spontaneous hemopneumothorax, the second, diagnosed clinically as a spontaneous hemothorax, but proved on bacteriological study to have been caused by tuberculosis, the third also simulated spontaneous hemothorax, but was proved subsequently to have been due to neoplasm. In the first true spontaneous hemopneumothorax, 1,800 cc. of dark brown fluid were aspirated two days following a typical history of the occurrence of sudden severe chest pain. The bloody fluid did not clot on standing and was

sterile. Oxygen lavage was followed by rapid reëxpansion of the lung, but a small amount of fluid had to be aspirated forty-eight hours later. On complete reëxpansion, several emphysematous blebs were demonstrated. Blood should be aspirated to prevent the organization of fibrin with the formation of pleural adhesions and marked pleural thickening leading to incomplete reëxpansion with its attendant retraction of the heart, lung, and retraction to the affected side.—*Spontaneous Hemothorax: A Discussion of the Problem Based on Three Cases*, A. Bernstein, E. Klosk & A. E. Parsonnet, *Dis. of Chest*, September-October, 1946, 12: 394.—(K. R. Boucot)

Bilateral Spontaneous Pneumothorax.—Simultaneous bilateral spontaneous pneumothorax is relatively uncommon. A case is reported in a soldier. He awoke that day with a slight pain in the right chest. Symptoms became well established when he assumed duty. In the afternoon he reported to the outpatient department, where the pneumothorax was discovered. Previous history was not significant. X-ray confirmed the diagnosis of a complete right pneumothorax. Two days later, when using a bedpan, he experienced a severe pain in the left chest. He rapidly became cyanosed and dyspneic. Examination revealed the bilateral pneumothorax; 1,200 ml. of air were removed from each pleural cavity several times. A simple device of a French blood-transfusion needle which passed through the centre of a rubber diaphragm was inserted through each anterior chest wall and the patient was left for the night. The needles became blocked and he unfortunately developed some emphysema of the chest wall. Needles were removed the next day. He was placed on sulfadiazine in anticipation of an infection from the frequent needling of the chest. Both lungs expanded. Several theories of the cause of simultaneous bilateral pneumothorax are discussed. It is thought that occasionally an orifice in the mediastinum may be present which would permit passage of the air from one pleural space to the other. The prognosis of such a condition in tuberculosis is very poor, whereas

in idiopathic cases the result is usually complete recovery. In this case there was no evidence of pneumoconiosis or lung infection, and hence it was classified as idiopathic.—*A Case of Bilateral Simultaneous Spontaneous Pneumothorax*, G. M. Komrower, *Brit. M. J.*, April 12, 1947, 4501: 488.—(R. W. Clarke)

Pleural Empyema.—Chronic empyema can develop in cases treated either medically or surgically. It is the result of incomplete expansion of the lung due to (1) bronchopleural fistula, (2) thickening of the pleura or (3) atelectatic fibrosis of the lung. At first the fibrin deposits on the pleura are unorganized; organization occurs later. Whereas deposits on the parietal pleura can become quite thick, those on the visceral pleura remain thin. The prevailing view is that the pulmonary atelectasis is the result of compression by the pleural effusion. The author does not believe that this is entirely so. He feels that bronchial obstruction due to kinks or retained secretions is an important factor. This is seen in pathological specimens. Roentgenograms show variations in the degree of collapse in different parts of the lung, even in the absence of adhesions, indicating scattered bronchiolar obstruction. If this persists too long, irreversible changes take place. The inflammatory process extends into the interlobar septa resulting in fibrosis. The atelectasis *per se* also invites fibrosis. Purely medical treatment with antibiotics may result in elimination of the infection but not of the residual empyema, because of either insufficient aspiration or pocketing of the fluid. Incomplete expansion of the lung may be combated by deep breathing exercises. Thanks to the early elimination of toxemia by the use of penicillin, these may now be started early enough to be of value.—*Atelectasis as a Factor in the Medical Treatment of Pleural Empyema*, F. Fleischner, *New England J. Med.*, April 17, 1947, 236: 566.—(A. G. Cohen)

Gingival Biopsy in Amyloidosis.—The Congo red test is subject to false positive results, and a negative test may occur in patients with

moderate involvement. Visceral biopsy is limited. Generalized amyloidosis is characteristically most abundant in perivascular tissues. Since the gingivae are highly vascular, easily accessible and markedly resistant to infection, this tissue has been used for biopsy. Patients selected for this study were from three groups: those with clinically diagnosed amyloidosis, those in whom the diagnosis was suspected and an apparently normal group. Gingival tissue, about 3 x 5 mm., was excised without any important complications. Preliminary findings indicate that the gingival tissue may not contain amyloid changes, even though liver and spleen biopsies do. Gingival biopsies often show amyloid in the absence of any of the usual clinical signs of the disease.—*Gingival Biopsy for the Diagnosis of Generalized Amyloidosis*, I. J. Selikoff & E. H. Robitzek, *Quart. Bull. Sea View Hosp.*, October, 1946, 8: 310.—(P. Q. Edwards)

Q Fever.—An outbreak of Q fever occurred in stock handlers and slaughterhouse workers in Amarillo, Texas, in 1946. There were 55 cases, 18 of which had to be hospitalized. Onset was with headache, chilly sensations, general malaise and sometimes nausea. There were few if any symptoms referable to the respiratory tract. More than half of the patients experienced thoracic pain of a neuralgic character. Roentgenological examination of the chest was the main source of evidence of pulmonary lesions. The lesions were the patchy type seen in bronchopneumonia. There was little correlation between the severity of illness and the degree of pulmonary involvement. Roentgenological evidence of pulmonary lesions was obtained in 11 patients. The treatment was supportive, chemotherapy being of no avail. Most patients made an uneventful recovery. Two patients died.—*Q Fever in the United States: II. Clinical Data on an Outbreak among Stock Handlers and Slaughterhouse Workers*, J. V. Irons & J. M. Hooper, *J. A. M. A.*, March 22, 1947, 133: 815.—(H. Abeles)

Fracture of First Rib.—So far only about 50

cases of fracture of the first rib have been reported in very few of which the cause was a violent coughing attack as in the present case. A contralateral thoracoplasty with removal of the first four ribs had been performed fourteen days before. While some serious and even fatal cases have been reported, the injury healed in this case within sixty days.—*Fratura isolada da primeira costela*, J. M. Castello Branco, *Clin. tisiol.*, July-September, 1946, 1: 247.—(A. A. Moll)

Official Tuberculosis Control.—Why did it take fifty-two years from the first organization of an unofficial tuberculosis association, the Pennsylvania Society for the Prevention of Tuberculosis, to the establishment in 1944 of the official Tuberculosis Control Division of the United States Public Health Service. The answer is that throughout this period conflicts existed between the medical and social approaches, the private and the public handling, the local and the central control of the disease. There was in the beginning the struggle of the concepts of the "contagiousness of consumption" against that of the heredity of tuberculosis. Many conflicting medical concepts and their practical application, the emerging of the social aspects of the problem about 1902, marked by the election of a layman as secretary of the Committee on Tuberculosis of the New York City Charity Organization Society, several attempts to organize a tuberculosis movement on a national scale—all these efforts sharply define the conflict between the private medical support for treatment and the public health belief in prevention. The foundation of the National Tuberculosis Association in June, 1904, signifies a compromise. The including of treatment and prevention in the objectives of the association meant close team-work between the medical profession and the public. The general acceptance of private control of the movement showed the distrust for the official health authorities, most of them being regarded as political appointees. Not until 1913 did the National Tuberculosis Association begin to discuss the place of local and

ABSTRACTS

State health departments in the tuberculosis movement, but several bills introduced in 1917 and 1918 in Congress to provide for a division of tuberculosis in the U. S. Public Health Service failed to pass. In 1919, under the impetus of World War I, the National Tuberculosis Association adopted a resolution urging the establishment of such a division, but no steps were taken to implement the idea. The migration of population that took place in the United States between World Wars I and II and increased in World War II brought about agitation for Federal aid in meeting cost for non-resident tuberculosis patients. Soon after Pearl Harbor, Surgeon General Parran established a small tuberculosis control section in the States Relations Division of the Bureau of State Services. In 1943 the National Tuberculosis Association appointed a War Emergency Committee which recommended participation in the Tuberculosis Control program by the United States Public Health Service, and this was supported by a mass education campaign carried on by every State tuberculosis association. Early in 1943 a comprehensive health bill was adopted by Congress, and on July 1, 1944, the Tuberculosis Control Division of the United States was established. At present, all the most enduring functions of the unofficial tuberculosis organizations in experimentation, demonstration, legislation and education are fundamentally directed toward the building of adequate public support for official tuberculosis control.—*The Evolution of Tuberculosis Control in the United States*, R. G. Paterson, *Pub. Health Rep.*, March 7, 1947, 62: 336.—(O. Pinner)

Tuberculosis Mortality 1945.—During the four years of World War II the tuberculosis death rate for the United States declined as rapidly as in the four preceding years. There were 52,916 deaths from all forms of tuberculosis in the continental U. S. in 1945, the death rate was 40.1 per 100,000 as compared with 41.3 for 1944. This figure decreases to 38 when the overseas American population with 72 deaths is included. The death rate,

computed on this latter basis, decreased 5.3 per cent from 1943 to 1944, and 4 per cent from 1944 to 1945. The death rates for white females and non-whites of both sexes continued to decline, that for white males showed little change. The death rate for the white population was 32.7; the rate for Negroes was 98, for Japanese 101.5, for Indians 211.9, for Chinese 267.1. In all race groups the rates for males were higher than for females; in all race-sex groups the rates increased with age after the age of 5. In 1945, there were 4,437 deaths among veterans of all wars, 62.8 per cent of World War I, 31.4 per cent of World War II. In 1944 the latter group had contributed only 22.3 per cent, and the number of deaths among them increased from 974 in 1944 to 1,394 in 1945. This increase in the proportion of World War II veterans is due to a decrease in the number of deaths among World War I veterans, as well as to the increase in the number of deaths among World War II veterans; further increase of this proportion must be expected. The death rates for the 48 States and the District of Columbia ranged from 10.9 for Wyoming to 123.1 for Arizona. There is, like in previous years, an area of low mortality extending from the Pacific Northwest to the Great Lakes and an area of high mortality extending from the Southwest to the Atlantic coast. For 36 States the rates were lower in 1945 than in 1944, for 11 States higher and for 2 the same. Tuberculosis of the respiratory system accounted for 92.4 per cent of all tuberculosis deaths. Nonrespiratory forms constituted 9.6 per cent of all tuberculosis deaths among non-whites and 7 per cent among whites. Of them, more than one-quarter were from tuberculosis of the meninges and central nervous system, and about one-quarter from disseminated tuberculosis. The death rates for nonrespiratory tuberculosis ranged from 0.8 for Wyoming to 8.4 for New Mexico.—*Tuberculosis Mortality in the United States and in Each State: 1945*, E. H. Pitney & R. V. Kasius, *Pub. Health Rep.*, April, 1947, 62: 487.—(O. Pinner)

Tuberculosis Control.—The natural decline of tuberculosis rates within the past thirty years and the application of better control measures have brought about a profound modification of this disease. In Switzerland, 50 per cent of young people are still tuberculin-negative at the age of 18. This desirable result of control measures brings with it renewed dangers, as it is clear that one open case among tuberculin-negative people can start a small epidemic. The answer to this threat lies in the application of yet more effective methods of case-finding to detect the open case, and in stringent control of known positive cases. Those who doubt that eradication of tuberculosis can ever be accomplished doubt the wisdom of aiming at a low primary infection rate. They feel that primary tuberculous infection is necessary for protection from postprimary disease, and that delaying the date of primary infection in children and young people means added hazards when these people are forced to earn a living in a community which necessarily includes open tuberculous cases. The author feels that in Switzerland it is entirely practicable to work towards eradication of the disease if enough funds could be expended to find the open case. Any such program should include an improved plan of therapy, and a harmless but effective method of immunizing tuberculin-negative cases. BCG does not entirely fulfill this demand. In spite of its relative value, it is less effective than a true primary tuberculous infection in preventing superinfection, because typical primary infection has occurred in BCG vaccinated individuals. In favor of BCG is that the danger of endogenous reinfection does not follow its use. Incidentally, the author condemns the practice of tuberculosis resorts to cater to healthy people in search of recreation in winter sports. Many thousand tuberculin-negative youths gather annually in such resorts where they are exposed to heavy infection by open tuberculous cases who mingle freely with tourists.—*Wo stehen wir in der Tuberkulosebekämpfung*, E. Sommer, Schweiz.

med. Wchnschr., October 26, 1946, 76: 1099.—(H. Marcus)

Tuberculosis Death Rates in Buenos Aires.—While tuberculosis is by law a notifiable disease in Argentina, this provision remains to a large extent a dead letter. In a disease, such as tuberculosis, with a protracted course, intercurrent conditions and complications lend themselves to falsification of the true nature of the cause of death. In Buenos Aires the problem is further involved by the afflux of patients from the interior of the country in search of treatment, dying away from home. Available figures for the years 1925 and 1945 show a decreasing death rate for pulmonary tuberculosis from 173 to 82 per 100,000, while the general death rate declined from 13 to 11.4. Pulmonary tuberculosis, which was charged in 1925 with 13.2 per cent of the general death rate, by 1945 represented only 7.2 per cent of the total. The available data suggest Buenos Aires is now entering the "detuberculization stage" as has been the case with many other cities in the United States and England. While, in 1925, 50 per cent of the tuberculosis deaths occurred in men under 33 and in women under 25, by 1945 this load had moved to a more advanced age: 38.8 years for men and 27 years for women. The change was not parallel for both sexes and was much more marked among males. The death age which averaged 28 years among women and 34 years for men in 1925 became 30.5 and 38 years, respectively, by 1945.—*Variaciones de la tasa de mortalidad por tuberculosis pulmonar en la Capital Federal en el transcurso de los últimos veinte años*, R. A. Izzo & A. Chouela, *Pub. del Centro de Investig. Tisiol.*, 1946, 10: 189.—(A. A. Moll)

Antituberculosis Campaign in Peru.—The number of deaths from tuberculosis reported in recent years in the 16 largest cities in Peru were: 1942, 4,252; 1943, 4,593; 1944, 4,409; 1945, 4,433. The death rates varied from 1,090.4 per 100,000 in 1943 in Tacna, to 157 per 100,000 in Cuzco in 1942. The rate for

Lima averaged 362 in the four-year period. In the localities so far surveyed, tuberculin tests have proved positive in 50 per cent of children under 17, and 85 per cent in persons between 17 and 60, and 35 per cent among infants. Inapparent infection rates among apparently healthy persons have totaled 3 to 5 per cent and active infection in suspected cases 16 per cent. Highest infection rates correspond to infants and the 20 to 24 age period. BCG vaccination was started in 1934 and the tuberculosis division in the National Department of Health was organized in 1937 and enlarged in 1941. It now includes local services in various areas in the country. The work is being developed along the recognized lines of tuberculin and X-ray surveys, dispensaries and mobile X-ray units, hospitals, sanatoria, and preventoria. Present plans embrace gradual increase of number of hospital beds to 6,470, and of dispensaries to 14, operation of six tuberculosis units in the largest cities, and training of social service personnel. Funds available in 1946 added up to 5,392,000 soles (about \$485,280), which included the revenue derived from tuberculosis seals. In addition, a loan of 20,000,000 soles (about \$1,800,000) has been authorized for building sanatoria. The number of patients found by the dispensaries has increased from 2,878 in 1940 to 6,731 in 1946, and the number of persons examined, from 13,065 to 87,483.—*Cómo Desarrolla el Departamento de Tuberculosis de la Dirección General de Salud Pública el Programa de Control de la Tuberculosis, L. Cano Girona, Rev. tuberc., (Lima, Peru), July-December, 1946, 6: 817.*—(A. A. Moll)

Tuberculosis Mortality in French Cities.—Study of the tuberculosis mortality in the large French towns in 1946 reveals a considerable decrease as compared to the rates of 1945. The latter had already shown a decline in comparison to the period 1934-1936.—*La mortalité par tuberculose dans les grandes villes françaises en 1946, A. Lotte, Mme. F. de Chambrun & M. Moine, Bull. Inst. Nat. d'Hyg., January-March, 1947, 2: 2.*—(V. Leites)

Tuberculosis in Sanatorium Employees.—While there are numerous reports concerning tuberculosis among student nurses and also other employees in general hospitals, reports are few concerning the employees of tuberculosis sanatoria. The author studied 1,000 employees of the Carlo Forlanini Institute from 1935 to 1944. During this period he observed 18 pleural effusions and 76 cases of pulmonary tuberculosis. Of the latter, complete data were available for those from 1938 on, namely, 56 cases. These are analyzed from the standpoint of clinical forms of the disease. Nine cases had an acute onset of influenzal type with fever, asthenia, joint pains and upper respiratory symptoms; the X-ray films showed one tuberculous pneumonia, 2 cases of nodular foci with rapid confluence and liquefaction, and 6 early infiltrates. Forty-seven cases had an insidious onset; 25 of these had slight toxemic symptoms, 13 moderate, 2 had hemoptyses, 3 had symptoms of toxemia with negative films which later became positive, and 4 had X-ray findings only. The analysis of symptoms in order of occurrence showed that fatigue, anorexia, indigestion, work intolerance and menstrual abnormalities came early; cough, dyspnea and chest pains were next noticed; and fever and loss of weight came later. The X-ray film of the 47 cases showed 3 fugitive infiltrates of the Loeffler type, 10 perifocal exudates near old healed nodules, and 34 new infiltrates. The infiltrates were definitely of exudative type, usually apical in location and described as polymorphous, of moderate or slight density, with indefinite or "unraveled" margins. These 34 were considered essentially chronic type. Most of the employees promptly improved upon rest treatment.—*Forme Cliniche di Tuberculosi Polmonari in un Gruppo di Soggetti Addetti a Servizi Sanatoriali, G. Babolini, Arch. di tisiol. (Napoli), January, 1946, 1: 35.*—(E. Kupka)

Tuberculosis Survey in Switzerland.—A tuberculosis case-finding program was initiated in 1946 by the *Industrierverband* (industrial association) of the Canton Zug, in Switzerland.

Zug is a small canton with 38,000 inhabitants, but a considerable number of important industrial enterprises and institutions are located there. X-ray films were taken of 4,180 people, most of whom were employed in industry. Participation was voluntary, but the management of the participating firms and institutions attempted to get coöperation by setting an example, and by explanatory talks. In all, 230 cases demonstrated abnormalities in their chest films, and 95 of these showed significant tuberculosis. Further breakdown of this last figure showed that there was one case of hitherto unknown open tuberculosis, 4 of known active but closed tuberculosis, 19 of unknown active closed disease, 50 of inactive closed disease hitherto unknown, and 21 of inactive closed known disease. Other conditions detected in this survey were 22 cases of intrathoracic goiter, 2 foreign bodies in the lung, 2 cases of sarcoidosis, one case of silicosis, one case of bronchiectasis, and 14 cases of chronic bronchitis and emphysema. There were 178 cases showing evidence of old scars and calcifications, presumably tuberculous. The preceding figures demonstrate the superiority of case-finding by X-ray surveys over any other known method. To aid in the eradication of tuberculosis, the author pleads for restriction of tuberculous foreign patients to institutions designed for the treatment of tuberculosis. He feels that the Swiss population is significantly endangered by the influx of foreigners who come to Switzerland to take the "cure," but who are permitted to move about the country with the freedom of the tourist.—*Schirnbildaktion des Zuger Industrierverbandes im Januar/Februar 1946, O. Weber, Schweiz. med. Wchnschr., February 22, 1947, 77: 264.*—(H. Marcus)

Tuberculosis Control in Shanghai.—The first step in tuberculosis control was undertaken in Shanghai in August, 1929 when the Municipal Health Department opened a tuberculosis sanatorium. Since then steady progress has been made in this work, the most important step having been the organization, in November, 1938, of the Shanghai Anti-

tuberculosis Association which, since 1942, has operated the largest up-to-date tuberculosis hospital in Shanghai, devoted only to charity cases. Before the war 6 per cent of the population was estimated to have tuberculosis of some form. This number has increased after the war to 8 per cent or 240,000 persons with probably no less than 10,000 annual deaths. The mortality has risen from 1,161 in 1937 to 4,503 for 1941 and 2,269 for the first six months of 1942. Tuberculosis is the major cause of death in Shanghai.—*History of Tuberculosis Control in Shanghai, L. S. Huizenga, Chinese M. J., January-February, 1947, 65: 1.*—(O. Pinner)

Tuberculosis in Concentration Camps.—This work summarizes the experience with 243 people liberated from concentration camps, and with 53 foreign workers. These 296 people were examined at Herisau, and following the discovery of the appalling prevalence of tuberculous disease in this group hospital facilities were hurriedly provided. Of the group of 243 former inmates, only 106, or 44 per cent, were free from pulmonary tuberculosis. Twenty-five, or 10 per cent, showed inactive tuberculosis, and 112, or 46 per cent, showed active disease. Of the foreign workers, 12 showed active and 2 inactive disease. Of a small group of 13 Spaniards, only 2 were free from tuberculosis. Active tuberculosis was, therefore, found about 200 times as frequently in this small group than in a population at large. Inactive disease was found 13 times as frequently as in the general population. Study of this group of inactive cases showed that it is extremely unlikely that any of these cases contracted and healed tuberculous disease while imprisoned. It is concluded that they represent a selected group of people who had tuberculosis prior to incarceration, and their healed disease protected them from superinfection. As far as could be judged, there were 58 cases of active primary disease and 122 cases of active postprimary disease. There were 10 deaths in the primary group, and 5 in the postprimary group. Most of the

patients were in very poor condition on admission, and showed extensive bilateral disease with marked exudative lesions. Both groups responded extremely well to treatment in proper surroundings. The improvement was much greater than could have been anticipated from observation of equally bad cases under the usual living conditions. Deprivation and starvation apparently do not cause breakdown of endogenous tuberculous foci, but the staggering incidence was solely due to massive exposure. Failure of the inactive cases to break down under these conditions again bears out this conclusion. Because the prognosis of even hopeless appearing cases became favorable with proper management, the tuberculosis rate in Europe need not necessarily rise too high. The main problem is to detect and isolate the open case. Starvation in itself does not produce tuberculosis.—*Gestalt und Frühverlauf der Tuberkulose bei Patienten aus Konzentrationslagern*, A. Zuppinger & A. Labhart, *Schweiz. med. Wchnschr.*, January 25, 1947, 77: 144.—(H. Marcus)

Apical Pulmonary Tuberculosis.—Older theories regarding the localization of tuberculous lesions are not in agreement with the results of animal experimentation. Neither can Roder's theory of increase in hydrostatic pressure be justified. The work of Cournand and Richards has shown that the systolic pulmonary arterial pressure is 18 to 30 mm. of mercury in the recumbent posture and is less when sitting or standing, especially in persons who move but little while in these positions. Since there is a fall in pressure along the course of a vessel the blood flow, formation of lymph or tissue fluid must be very slow in the upper third of the lungs. The right pulmonary artery being more tortuous, the systolic pressures will be lower on this side, and the relatively bloodless region larger than on the left. Thus inadequate pulmonary blood flow especially in sedentary persons, and those obtaining insufficient sleep, may account for the relatively high resistance of the lower position of the lung, and the tendency to progression of disease in one or both

lung fields highest above the heart. Alveoli aerated through bronchi but deprived of normal blood flow will have the highest oxygen and lowest carbon dioxide content. Such a state favors the growth of tubercle bacilli. It is possible that relative ischemia may be conducive to accumulation of toxins, decreased antibody content and reduced phagocytosis. Tests of a conclusive nature, which could be done by injection of small quantities of radioactive isotopes, have not been done, hence the above assumptions are purely speculative. However, the low incidence of pulmonary tuberculosis in mitral stenosis and the high incidence in those with pulmonic stenosis are factors in support of this theory. This thesis would make absolute recumbency imperative regardless of the locale of the patient and would suggest that short periods of activity would not be deleterious.—*Reasons for the Common Anatomic Location of Pulmonary Tuberculosis*, W. Dock, *Radiology*, April, 1947, 48: 519.—(G. F. Mitchell)

Inapparent Tuberculosis.—In mass X-ray surveys in Rio de Janeiro, between 1 per cent and 3 per cent of all examined had non-apparent tuberculosis. Amongst the individuals exposed to contact, the incidence of active tuberculosis accidentally found in the survey was 5 to 12 per cent, which is 5 to 6 times higher than in the remainder of the population. For Rio de Janeiro, amongst 96,467 examined, 3,375, or 3.51 per cent, had tuberculosis. About half of these were in an active stage. The percentage of persons with positive X-ray findings was for San Pablo 2.02 per cent; for Porto Alegre 8.49 per cent; for Bahia 11.52 per cent. For all cities of Brazil, the incidence of tuberculosis among more than 175,000 surveyed people was 4.46 per cent, of which 2.18 per cent had active and 2.28 per cent had inactive tuberculosis. Approximately the same result was obtained in other countries of South America. The incidence of tuberculosis was highest among professional men and public servants. The use of photofluoroscopy and small film survey enables the detection of tuberculosis in a

relatively high percentage of supposedly healthy people. A complete review of all available statistics of the frequency of inapparent tuberculosis is given.—*Frecuencia de la tuberculosis inaparente*, A. de Paula, *Prensa méd. argent.*, August 30, 1946, 33: 1787.—(W. Swienty)

Tuberculosis after Forty.—Among 217 cases of pulmonary tuberculosis in patients over 40 years old, 111 were in men and 106 in women. As in other series reported in the literature, the fibro-caseous type prevailed (156, as compared to 36 exudative and 25 fibrotic cases). This disproves contentions that a fibrotic pattern is characteristic of senile tuberculosis. Neither did the so-called "outburst" of tuberculosis among people in the forties find any support. Among both exudative and fibrotic cases the outcome became more serious as age advanced, but the number of patients was too small to justify definite conclusions, especially as to the former group. In fibro-caseous cases prognosis proved usually unfavorable, with little difference traceable to age. Among the 45 fatal cases in women the duration of the disease averaged twenty-one months and in 57 men twenty-four months, averaging twenty-two months for the entire series. A relationship to a preëxisting diabetes was apparent in women (in 29 out of 51 cases), especially after 50. For men, the rate was much lower. Fatal hemoptysis was also much more common with diabetes (in 6 out of a total of 11 cases). The rôle of intimate contact with patients was obvious in a moderate proportion of the whole group. Collapse therapy was generally well tolerated, but its success was not so apparent, the very worst results being in the 40 to 49 age period.—*La tuberculosis pulmonar después de los 40 años*, R. Rossi, *Pub. del Centro de Investig. Tisiol.*, 1946, 10: 81.—(A. A. Moll)

Retracted Lung Stump.—The above name is proposed as more adequate for the condition variously designated as rigid and unexpandable lung. Three cases are reported and

causation is discussed. Parenchymal fibrosis and a thickened visceral pleura being the predominating causes. Bronchial, parenchymal and pleural factors may bring about retraction of the pulmonary stump, but effusions, as a rule pleural, or a result of fistulous tracts, are most frequently at fault. Cases may develop after both artificial and spontaneous pneumothorax.—*Muñón pulmonar retraído postneumotorácico*, A. Molina & P. Sprinsky, *Pub. del Centro de Investig. Tisiol.*, 1926, 10: 241.—(A. A. Moll)

Inspissated Cavities.—Inspissated cavities seem to be uncommon in pulmonary tuberculosis. The largest series (23 cases) so far reported was from Chile (1943). Among 865 patients treated in a Lima dispensary only 5 cases were found. In this group inspissation invariably occurred in early cavities with thin walls and not exceeding 20 mm. in diameter. Blockage of the draining bronchi plays an important pathogenic rôle. The most frequent seat was the external subclavicular area. Diagnosis depends on previous presence of a cavity and its replacement, as shown by X-ray films, by an opaque rounded mass. While roentgenological, and even clinical, improvement accompany the development of inspissation, it should not be interpreted as evidence of permanent healing. Watchful waiting is indicated, with surgical measures to be applied if signs of renewed activity develop.—*Cavernas empastadas*, R. Vargas Machuca, *Rev. tuberc.*, (Lima, Peru), July-December, 1946, 6: 751.—(A. A. Moll)

Tuberculosis and Coccidioidomycosis.—The coexistence of active tuberculosis and coccidioidomycosis is rare. In a 27-year-old white soldier the diagnosis of coccidioidomycosis had been made in September, 1943 by roentgenological and sputum findings; after five months he had been discharged as apparently cured. In August, 1945 he developed a right hydropneumothorax. Examination of the pleural fluid showed tubercle bacilli on direct smear. Culture of the pleural fluid and guinea pig inoculation revealed the

presence of *Coccidioides immitis* and tubercle bacilli. "It is possible that a subpleural tuberculous cavity had ruptured into the pleura, with a resultant bronchopleural fistula, and that during this process extension into a well localized and latent coccidioidal infection had occurred."—*Coexisting Tuberculosis and Coccidioidomycosis*, H. Rifkin, D. J. Feldman, E. Hawes & L. E. Gordon, *Arch. Int. Med.*, April, 1947, 79: 381.—(G. C. Leiner)

Tomography in Pulmonary Tuberculosis.—A review of basic roentgenographic considerations, and of the physical and technical principles of tomography (laminagraphy) are presented. The lung section at the level for which the tomograph is set appears sharply defined while the X-ray image of parenchyma above or below the respective level is underexposed and indistinct. Thus, the desired layer of parenchyma is visualized free of superimposed structures. In determining the exact localization of cavities, or the type and extent of a contemplated thoracoplasty, or the possible establishment of a Monaldi drainage, tomography has proved most valuable. Applied in infiltrative, non-cavernous cases of tuberculosis tomography has helped to analyze the complex opacities of the conventional film. It was found in some instances that lesions at one level were of recent, at others of an old fibrotic type, while the usual film showed a uniform appearance of the disease. Tomography is considered essential, therefore, in appraising age, resolution or healing of tuberculous lesions.—*Die Bedeutung der Tomographie für die Beurteilung der Lungentuberkulose*, E. Haeflinger, *Gegen die Tuberk.*, January, 1947, No. 1.—(B. Gerstl)

Tuberculosis on Separation.—A report is given of a survey which includes the entire output of an Air Force Auxiliary Separation base which included practically all nationalities and races. In all, 24,615 men were examined, 23,537 of whom had no sign of any "significant chest abnormality." The find-

ings are consistent with those on the induction examinations; both active and apparently healed tuberculous lesions are comparatively few. There was a total of 1.09 active cases per 1,000 men which is higher than might be expected, but lower than on pre-induction examination. Other diseases of the pleurae and lungs were found and are about the same as in other surveys. All men deferred because of chest abnormalities are in the 18 to 24-year age group. Whether the active tuberculous cases represent new or recurrent disease is a question meriting investigation. Since many had no induction X-ray films there were no cases of primary type disease and none of the active cases had miliary calcification in the parenchyma, it is believed that the disease was probably not acquired in the Army.—*A Study of 24,615 Separation Chest Roentgenograms*, B. J. O'Loughlin, *Radiology*, April, 1947, 48: 389 —(G. F. Mitchell)

Chest Fluoroscopy.—The first phase of fluoroscopy is inspection of the diaphragm and bases of the lungs. The patient breathes deeply and is rotated 45 degrees from one side to the other. A medium-sized diaphragm is used. The second phase is inspection of the heart and mediastinum and of the general configuration of the chest, using a medium-sized or wide diaphragm. The technique is the same as during the first phase. The third phase is inspection of the lungs, especially the apices. A smaller diaphragm (about 10 x 15 cm. or less) is used. The patient is held by his arms, the shoulders are pulled down and forward and the patient is rotated to visualize any part of the apex. Fluoroscopy is superior to standard films in diagnosing apical tuberculosis, in detecting pleural fluid, disc-shaped atelectasis, various hidden pulmonary lesions and in the differential diagnosis of supraclavicular lymph node calcifications and apical calculi.—*The Technique of Chest Fluoroscopy*, L. Walk, *Acta radiol.*, 1947, 28: 14.—(J. E. Farber)

Pendular Movement of Diaphragm.—An analysis of the phenomenon of Holzknecht-

Jacobson is given. It is frequently seen in bronchial stenosis. The inspiratory deviation takes place towards the side of obstruction. In the conditions due to bronchial stenosis there is usually a permanent displacement of the mediastinum which represents its new position of equilibrium, upon which the inspiratory deviation of the mediastinum is superimposed. Thus, in atelectasis due to bronchostenosis there is a permanent displacement of the mediastinum towards the side of atelectasis. Inspiration increases the displacement in the same direction. In obstructive emphysema the mediastinum is displaced towards the healthy lung, but during inspiration there is a movement of the mediastinum towards the side of stenosis. The pendular movement of the mediastinum is less clearly visible in atelectasis than in obstructive emphysema, since the border of the mediastinum is projected partly into the vertebral column, partly into the opaque atelectatic lung. In stenosis without check-valve mechanism the mediastinum is not permanently displaced but remains in its normal median position and the Holzknicht Jacobson phenomenon can be observed in its pure form. The essential cause of the sign is seen in the fact that the involved lung does not react like a dilatable and elastic organ, but like a rigid block which does not vary its volume and which, when following the movements of the thoracic cage, draws the mediastinum in its direction. Besides the rigidity of the involved lung two other conditions are necessary to produce the Holzknicht-Jacobson phenomenon: A sufficient respiratory mobility of the hemithorax on the side of stenosis. In certain cases of atelectasis with complete immobilization of the thoracic cage on that side, the sign is absent. The second condition is the flexibility of the mediastinum making its displacement possible. The Holzknicht-Jacobson phenomenon cannot any more be considered as pathognomonic of bronchial stenosis. It has also been observed in cases of pleural symphysis and in acute consolidations of the lung. In both cases the introduction of air into the involved lung is abolished or

impaired which produces a state of inspiratory disequilibrium. Four case reports are given in which the phenomenon was due to bronchial stenosis in primary tuberculosis.—*Le mouvement pendulaire du mediastin ou phénomène d'Holzknicht-Jacobson*, M. Levrat, P. Galy & P. Martin-Noël, *Rev. de la tuberc.*, 1946, 10: 127.—(V. Leites)

Clicking Pneumothorax.—Some patients with a small pneumothorax on the left side may be conscious of a curious clicking sound synchronous with the heart beat. With the aid of the stethoscope, it is heard in various situations on the left side of the chest, most often near the apex. It is sometimes audible at a distance from the patient. It disappears if the pneumothorax increases in size. It varies in intensity with the position of the patient. Eight cases are reviewed in which the patient subjectively noticed the sound. In 5, the sound was heard by auscultation also. In 2, there was associated pain. Three patients developed a total pneumothorax within a short time, resulting in disappearance of the sound. The click is different from the sound which is heard in interstitial emphysema. It is probably due to an air bubble in contact with a pleural adhesion.—*Clicking Pneumothorax*, A. P. Thomson, *Lancet*, May 10, 1947, 1: 631.—(A. G. Cohen)

Pneumothorax in Pleurisy.—In 39 patients with pleurisy the pleural fluid was removed and replaced with filtered air. Twenty-eight patients completed successfully the treatment. The total of evacuating punctures was 44 and the number of refills 84 (averaging 3 per patient). Rest is enforced until no more fluid is visible. Disappearance of fluid occurred on an average in fifteen days. The method was introduced a few years ago by García Rosell in Lima. Definite conclusions will be reported as soon as a larger number of patients has been treated.—*Resultados del tratamiento por pneumo-serosa*, V. M. Tejada, *Rev. tuberc.*, (Lima, Peru), July-December, 1946, 6: 789.—(A. A. Moll)

Fibrin Bodies.—Up to 1940 only 30 cases of intrapleural fibrin bodies in pneumothorax have been reported in the literature. Seven new cases are now described, all of them seen during the last four years. In 2 cases the bodies were free (floating), in one pedunculated, and in 2 sessile. These bodies, also called colloquially "pebbles" and "mice," are polymorphic, adjusting themselves to the shape of their localization. Their development seems sudden and in some cases they disappear spontaneously. In other cases they flatten themselves against the walls of the chest and roentgenographically they are classed as pachypleuritis. In one case examined pleuroscopically they looked like masses of snow.—*Cuerpos fibrinosos intrapleurales en el curso del pneumotórax, M. Espinosa Galarza, Rev. tuberc., (Lima, Peru), July-December, 1946, 6: 782.*—(A. A. Moll)

Phrenic Exeresis.—In 1939 Gramazio reported 106 cases of phrenic exeresis operated during the preceding five years, 54 with "good" results. Reviewing these 54 cases in 1945, there was no information regarding 13, but 20 had definitely relapsed. During the last five years, of another 106 patients who had thoracoplasty, 10 had had phrenic exeresis; of these 10, 2 had diffuse bronchopneumonic spread after thoracoplasty. Of the remaining 96 without phrenic, only 2 had this pneumonic complication. These findings indicate the failure of permanent healing, and likewise, the danger of thoracoplasty following phrenic exeresis. The permanent phrenic operation has lost ground markedly because of (1) the availability of major thoracic surgery in many cases; (2) failure of permanent healing; (3) increasing knowledge regarding the unfavorable effect upon the function of the lung; (4) the operation has become absolutely contraindicated if later thoracoplasty is anticipated. The indications for phrenic intervention are now limited to the following: (1) lower lobe disease on either side; (2) for apical involvement when the remainder of the lung is also involved (posthemoptotic dissemination) or

when thoracic surgery must be long delayed (temporary phrenic only); (3) to supplement artificial pneumothorax a) when adhesions are present, b) at time of abandonment, especially where fluid is present; (4) in extrapleural pneumothorax which is not completely efficient; (5) as an emergency measure for persisting gross hemoptysis. It is often useful to inject the nerve with alcohol first to note the functional effect before operating on the nerve.—*Nota Aggiornativa Sulle Indicazioni Della Frenicoexeresi, A. Sesti, Gior. ital. d. tuberc., November, 1946, 1: 77.*—(E. Kupka)

Pneumoperitoneum.—The author has observed that even small amounts of air in the peritoneal cavity give rise to considerable diaphragmatic elevation. To explain this phenomenon he has reasoned that normally the abdominal cavity contains no "empty" space. The abdomen is completely filled by the organs it contains, and the interior of the abdominal wall and the lower surface of the diaphragm are in intimate contact with the organs, separated from them only by a small amount of fluid. It is this capillary attraction which keeps the abdominal organs in intimate contact with the diaphragm. The ligaments and other supports of liver, stomach, etc. are sufficiently lax so that they cannot be thought of as holding the liver to the undersurface of the diaphragm. When air is introduced into the abdomen, it immediately rises and severs this capillary attachment between the organs and the diaphragm. The weight of the abdominal organs no longer "hangs" on the diaphragm, and the diaphragm, thus released, follows the opposing intrapleural pressure which sucks it into the chest. Normally there exists an antagonism between the intrapleural pressure, negative on inspiration, and the abdominal pressure, positive on inspiration. The introduction of air into the pleural cavity makes the diaphragm descend, because of unopposed abdominal pressure, and air in the peritoneal cavity elevates the diaphragm, because of unopposed pleural pressure. The accuracy of this reasoning was tested by in-

jection of air intraperitoneally into a fresh corpse. Roentgenograms taken before and after demonstrated that both diaphragms had risen considerably in the upright posture.—*Zur Wirkungsweise des Pneumoperitoneums*, K. Lenggenhager, *Schweiz. med. Wchnschr.*, March 1, 1947, 77: 288.—(H. Marcus)

Tuberculosis of Tonsils.—Tonsillectomy was performed on 85 out of 387 children with all forms of tuberculosis. The indication fell into one of three groups. In group 1 the adenoids were markedly enlarged causing mouth-breathing with the usual train of symptoms; in group 2 there was marked enlargement of the tonsils with frequent attacks of tonsillitis and pharyngitis, with or without cervical adenitis; in group 3 a presumptive diagnosis of tuberculosis of the tonsils was made because of a discrepancy between the child's general condition and the extent of the obvious tuberculous disease. The children in group 3 were often in poor general condition, had high sedimentation rates and did not gain weight and strength properly in spite of the fact that the evident tuberculous focus was retrogressive. In all these cases the tonsils were enlarged and appeared chronically inflamed, and often there was enlargement of the cervical lymph nodes. Tuberculosis of the tonsils or adenoids was found in serial section in 27 instances in this group of 85 patients. With the exception of 2 cases, the tuberculous foci consisted of small disseminated foci which showed little tendency to caseation. In these 25 cases the tuberculous process in the tonsils appeared to be part of a hematogenous dissemination. In 2 cases with extensive cervical adenitis with fistula formation, the tonsils were massively involved and the disease was probably primary in the tonsils. Removal of the tonsils appeared to cure the cervical adenitis. No serious complications were encountered. One child developed an exudative pleuritis four weeks postoperatively, but did well thereafter. On the other hand, improvement in general condition with weight gain and relative freedom from respiratory infec-

tion was observed in the majority of the tonsillectomized children.—*Tonsillektomie bei tuberkulösen Kindern*, E. Martens, *Schweiz. med. Wchnschr.*, January 25, 1947, 77: 146.—(H. Marcus)

Tuberculosis of Tonsils.—Focal infection of the tonsils has proved to be of great importance in such diseases as nephritis and rheumatic fever, but tuberculous infection of the tonsils as a cause of bone and joint tuberculosis in children has not been generally accepted. Primary tuberculosis of the tonsil does occur. The frequency of its occurrence has not been settled, and when tuberculosis of the tonsil is diagnosed it is hard to prove that it was the primary focus. Histologically, primary infection of the tonsil is usually found in the depth of the crypts, and tuberculosis of the draining cervical lymph nodes is frequent. In a recent study by Ellonen, tonsillectomy was performed on 74 children with bone and joint tuberculosis. None of these children had pulmonary tuberculosis, and only one an exudative pleuritis. Histologically tuberculosis was found in 20, or 27 per cent, of these patients, and it might be supposed that this figure would be higher if all of the tonsillar tissue removed could have been subjected to detailed histological examination. Ellonen argues that it is impossible for the tonsils to have become infected by the hematogenous or lymphogenous route from the bones and joints, and the tonsil must have been the primary focus. Tuberculosis of the tonsil cannot usually be diagnosed clinically, and it may be that many children who have positive tuberculin tests but no evidence of calcifications in the lung field or roent shadows have primary tuberculosis of the tonsils. All of Ellonen's cases were concerned with the human bacillus, since bovine tuberculosis is practically unknown in Finland, but it might be supposed that figures for tuberculous tonsillitis would even be higher in countries where tuberculous cattle abound. Clinically it has been observed repeatedly that tonsillectomy changes the progress of a child to a

favorable one after many months of standstill, and it is felt that all cases of children's tuberculosis ought to be seen by the otolaryngologist for evaluation of the tonsillar tissue.—*Tonsillen und Tuberkulose*, H. Vetter, Schweiz. med. Wchnschr., March 15, 1947, 77: 323.—(H. Marcus)

Bone and Joint Tuberculosis in Finland.—Finland introduced a pension law in 1939 including all individuals between 18 and 54 but excluding those unable to work. This led to extensive surveys concerning the morbidity of bone and joint tuberculosis. A total of 2,135 persons (one per cent of the population) were found to suffer of this disease, 63 per cent of whom needed hospitalization. The incidence is high when compared with western countries but lower than that of the Leningrad area. Therapy, in 60 per cent of the cases, was instituted only two years after onset of the disease and its results were highly unsatisfactory. Preventive measures and improvement of therapy are advocated.—*Die den Arbeitsunfähigen zuteil gewordene Behandlung*, P.E.A. Nylander, Ann. Chir. et Gynaecol. Fenniae, 1947, Vol. 36, Supplementum 1.—(B. Gerstl)

Resistance of Tubercle Bacilli to Streptomycin.—Tubercle bacilli isolated from guinea pigs inoculated with sputum, urine or material obtained on gastric lavage from tuberculous patients who were being treated with streptomycin are as resistant as cultures isolated directly from the same materials. Cultures of tubercle bacilli from patients receiving streptomycin retain their resistance to the drug even after residence in guinea pigs for ten weeks or more and subsequent maintenance on glycerinated egg-yolk agar for many weeks. Cultures from untreated tuberculous patients usually are resistant to only 0.08 to 0.62 μ g. of streptomycin per milliliter of medium and the majority to 0.15 μ g. After treatment some cultures are resistant to 2,000 μ g. of streptomycin.—*Persistence of Resistance of Tubercle Bacilli to Streptomycin*

during Passage through Guinea Pigs, A. G. Karlson, W. H. Feldman & H. C. Hinshaw, Proc. Soc. Exper. Biol. & Med., January, 1947, 64: 6.—(F. B. Seibert)

Streptomycin and Sulfones in Experimental Tuberculosis.—The chemotherapeutic effect of streptomycin combined with sulfone compounds was greater than the sum of the effects from the individual components. The chemotherapeutic effectiveness (ratio of extent of tuberculous involvement in a group of untreated controls and treated groups) in a group of guinea pigs treated with 40 mg. (40,000 units) streptomycin per kg. of body weight daily was 14.4. Treatment with 10 to 15 mg. per kg. per day under similar conditions gave a ratio of 5.2, and with 20 mg. streptomycin per kg. per day plus 500 mg. 4-amino-4'-propylamino-diphenylsulfone per kg. per day was 28.6. The chemotherapeutic effectiveness of the sulfone alone was 3.7. Similar but less marked effectiveness was obtained in combined therapy with streptomycin and 4-amino-4'-succinimidodiphenylsulfone and still less with sulfadiazine.—*Chemotherapeutic Action of Streptomycin and of Streptomycin with a Sulfone or Sulfadiazine on Tuberculosis*, M. I. Smith, W. T. McClosky, E. L. Jackson & H. Bauer, Proc. Soc. Exper. Biol. & Med., February, 1947, 64: 261.—(F. B. Seibert)

BCG in Russia.—Results of infant vaccination with BCG in the U.S.S.R., begun in 1924, have recently been made available. After a period of preliminary studies, the first applications of the vaccine were made in the Ukraine in 1926. Between 1926 and 1928, according to Medovikov, 818 infants in this region received BCG. In Leningrad, vaccinations were begun in 1928 and were extended in 1929 to four other large cities: Moscow, Saratov, Kazan and Rostov-on-the-Don. These cities were selected because of the presence of specialists qualified to use BCG under experimental conditions. In these five cities, 454 newborn infants received BCG in 1929. In Leningrad, 310 infants were vaccinated between 1928 and 1934. Meantime, in 1928, a BCG Commis-

sion was created to control this work. In Leningrad, among the 310 infants vaccinated, 87.6 per cent were in direct, intimate contact with tuberculosis. However, in this group, mortality was 4.3 per 100 compared with 16.4 per 100 in a control group of 79 non-vaccinated infants. Because of these results, the studies were extended to include 9,967 infants vaccinated in Leningrad between 1934 and 1936. Mass vaccination of the newborn was begun in 1937. During the first year of this campaign, 40,000 infants received BCG. In 1938, in Leningrad alone, 43,962 infants were vaccinated. From 1937 to 1940, inclusive, more than 2,000,000 infants were vaccinated throughout the country; in the larger cities, the percentage of vaccinated newborn infants exceeded 90 during 1940 and 1941. In almost all cases, the BCG was administered orally: 2 cc. in milk, 3 times, at forty-eight-hour intervals, or a single 3 cc. dose. Thirty-five per 100 vaccinations by the subcutaneous route were reported from the Leningrad series—all others being oral. All vaccinations were given during the first ten days of life. No mention is made of separating these infants from their tuberculous milieu. Local benign lymphadenitis was reported only in the Moscow group, where a different strain of BCG was employed. No case of cold abscess was found in the infants inoculated subcutaneously; incidence of lymphadenitis was 0.5 per 100 in the subcutaneous group; 2.6 per 100 in the oral group. Klebanov, reporting on the Moscow study in 1938, compared two groups of infants: 56,951 vaccinated, 17,469 not vaccinated. Both groups appeared healthy at the time of vaccination. Tuberculosis mortality in the vaccinated group at the end of one year was half that of the non-vaccinated controls. This result is the more remarkable in so far as the infants in the first group were exposed to a considerably greater degree of tuberculosis in the family. During the first six months of life, there was no appreciable difference between the mortality rates in the two groups of infants. Mortality rates after the second year were comparable to the one-year results. Morbidity rates for

this same series of infants revealed percentages similar to the mortality figures. Mass vaccination with BCG begun in 1937 in Moscow and Leningrad, at which time the infant mortality was at an index of 100, produced, after four years, a reduction in the index to 60, thus establishing the unquestionable efficacy of oral BCG vaccination for newborn infants.—*La prévention de la tuberculose par le BCG en U.S.S.R.*, S. A. Abolnick, *Ann. Inst. Pasteur, April, 1947, 73: 373.*—(P. Q. Edwards)

BCG in Leprosy.—In a preventorium in Paraguay 31 apparently leprosy-free lepers' children were inoculated with BCG using Rosenthal's technique. A previous tuberculin and photoroentgenographic survey had shown 77 per cent to be tuberculin-positive; some had primary lymph node involvement. In 20 of the group a previous negative Mitsuda test became positive after vaccination with BCG. In the other 11, in which the results of the Mitsuda test before vaccination were unknown, 82 per cent proved positive after vaccination with BCG. It is suggested that in endemic leprosy areas BCG might be considered for protection against leprosy if it is accepted that a positive Mitsuda test means relative immunity to leprosy.—*La reacción de Mitsuda en los vacunados con BCG: Posibilidad de la vacunación BCG en la profilaxis de la lepra*, A. R. Ginés & J. G. Poletti, *Mem. y Com. Sec. Prof. y Epidem. Tuberc.*, 1946, 4: 5.—(A. A. Moll)

Stain for Acid-fast Bacilli.—A new method is described for staining tubercle and leprosy bacilli, the bacilli of Johne's, Traum's and Gollerstedt's diseases, the acid-fast saprophytes, Moiser's "oval bodies" and, at least parts of the younger forms, of actinomyces and the common molds, such as aspergillus, penicillium and mucor. In a certain stage of their development, the spores of some bacteria, for example, *B. anthracis*, *B. subtilis* and *B. perfringens*, can be stained by this method. The dye *Nachtblau* (Grübler & Co.) which in watery solutions behaves like a colloid, is used

in combination with water, alcohol and phenol. There are two different procedures: the successive method in which *Nachtblau* is followed by counterstaining with pyronin, neutral red, carbol-fuchsin, vesuvin or Bismarck-brown; and the simultaneous method in which the staining solution contains both *Nachtblau* and pyronin. Tubercle bacilli are dark-blue and appear larger and more numerous than in Ziehl-Neelsen preparations; they have sharper outlines and stand out more clearly against the red or yellow background; all this makes them more easily detectable. In tuberculous sputa all the other organisms of the buccal flora take the counterstain with the exception of a yeast-oidium-like fungus which usually stains with *Nachtblau* like the tubercle bacilli. This fungus corresponds to that of Reenstierna (1912), found able to produce acid-fast rods with the same morphological and tinctorial qualities as those of the tubercle bacillus. Schaumann and Hallberg found fungus cells quite similar to those described by Reenstierna in *lymphogranulomatosis benigna*, together with other acid-fast forms. In pus from lymph nodes of guinea pigs inoculated with tuberculous material, acid-fast fungus cells were found with this staining method. The complete morphology of the causative agent of tuberculosis, leprosy and other diseases will be studied, since the classical bacilli are believed to be merely evolutionary stages originating from lower, commonly occurring fungi. (4 color plates)—*A New Method for Staining Tubercle Bacilli, Applicable Also to the Micro-Organism of Leprosy and Other Acid-fast Germs*, V. Hallberg, *Acta med. Scandinav.*, 1947, Supplementum 180.—(O. Pinner)

Papain for Sputum Digestion.—The use of papain, a proteolytic enzyme from the green fruit of the papaya, in the homogenization of sputum has proved to be of great value in simplifying the demonstration of tubercle bacilli contained in such sputum, by microscopic examination, culture or guinea pig inoculation. The technique consists of adding

0.05 to 0.10 g. of papain powder to 4 to 5 cc. of sputum. (Dissolve 20 g. of papain in 200 cc. of water at 20° C., filter, sterilize, store in the ice-box; 1 cc. of the solution is used as above.) The mixture is placed in a water-bath at 60° for forty-five minutes. Homogenization, which begins in fifteen minutes, is almost complete in twenty minutes, becoming of a water-like consistency. No alcohol is needed to enhance liquefaction. After centrifuging, the residue is smeared on a slide and stained by the usual Ziehl method. Preparations thus made reveal disappearance of most bacteria other than the tubercle bacilli, which retain their form and staining properties. Concentration of tubercle bacilli by this method is about 10 times that normally obtained; that is, sputum showing one bacillus per 10 fields by ordinary methods of preparation, show one bacillus per single field after this type of digestion with papain. Further advantage lies in the selective qualities of the papain digestion, as all other bacteria are apparently destroyed by the process. Culture and guinea pig inoculation of the residue reveal growth of tubercle bacilli, if present.—*Homogénéisation des crachats et des exsudats pathologiques par la digestion papainique en vue de la recherche du bacille de Koch*, P. Sédallian & R. Corraz, *Ann. Inst. Pasteur*, April, 1947, 73: 398.—(P. Q. Edwards)

Measurement of Growth of Tubercle Bacilli.—*M. tuberculosis* var. *hominis* H37Rv and No. 607, and *M. tuberculosis* *avium* were grown diffusely in Dubos' medium, containing Tween 80 and their rate of growth determined turbidimetrically with a Klett-Summerson colorimeter. A satisfactory turbidity was obtained with 1 mg. of cell material per milliliter, as checked by plate counts of viable bacteria. A standard curve was made in this way. Pathogenic strains grew at a slower rate than the saprophytes. The effect of nitrogenous materials on the rate of growth was studied and also the effect of streptomycin.—*Quantitative Measurements of Growth of Mycobacterium tuberculosis: Effect of Strep-*

tomycin, Dorothy G. Smith, *Proc. Soc. Exper. Biol. & Med.*, January, 1947, 64: 36.—(F. B. Seibert)

Demonstration of Acid-fast Bacilli.—A new method for bacterioscopic investigation of acid-fast bacilli in organic fluids and tissues is described. It is based on the method of Fernández and Olmos, which uses density differences to concentrate leprosy bacilli, and of Dharmendra, which uses chloroform extraction for the same purpose. Satisfactory results have been obtained in urine, sputum, pleural effusion, spinal fluid, gastric juice, and skin lesions (lupus vulgaris, tuberculoid leprosy), etc. The technique described is simple and more sensitive than those now in use. (Authors' summary)—*Nuevo método para la investigación bacterioscópica de bacilos ácido-resistentes*, M. Bergel, J. M. M. Fernandez & A. Serial, *Rev. méd. de Rosario (Argentina)*, January, 1947, 37: No. 1.

Pathogenicity of Tubercle Bacilli.—Antigenic complexes made by extracting H37Rv strain of human *M. tuberculosis* by means of trichloroacetic acid, trypsin digestion, diethylene glycol or urea appear to increase generalized infection in guinea pigs receiving very small numbers of organisms. It is suggested that such complexes may function as a "virulence factor" for the tubercle bacillus in a susceptible species of host.—*Pathogenicity of the Tubercle Bacillus*, S. Raffel, *Proc. Soc. Exper. Biol. & Med.*, April, 1947, 64: 507.—(F. B. Seibert)

Tuberculosis in Mice.—Mice, three to six weeks old, inoculated intravenously with 0.01 cc. of whole culture of H37Rv, grown seven to ten days on a medium containing 0.05 per cent Tween 80 and 0.2 per cent bovine albumin, and having an approximate density of 0.2 mg./cc., begin to lose weight during the second week after infection and die in three to four weeks with a disease primarily pulmonary. The infection is greatly enhanced by the addition of fresh egg-yolk to the cul-

ture. The H37Ra culture, however, fails to establish a progressive infection or to produce grossly visible lesions even with the addition of egg-yolk. Fifteen different strains of mice differed greatly in their susceptibility to tuberculous infection by the intravenous and intraperitoneal routes.—*Infection of Mice with Tubercle Bacilli Grown in Tween-Albumin Liquid Medium*, Cythia Pierce, R. J. Dubos & G. Middlebrook, *Proc. Soc. Exper. Biol. & Med.*, February, 1947, 64: 173.—(F. B. Seibert)

Vole Bacillus.—In the course of work with the vole acid-fast bacillus, the authors wished to use a more recently isolated strain. Two calves were given intravenous injections of 5 mg. of 7-day-old cultures. A similar dose of an older strain (LV 285) had been given to 142 animals without ill effects. One calf died in one month; the other became moribund in eight weeks and had to be slaughtered. In neither were there macroscopic lesions severe enough to cause death. However, there were wide-spread histological lesions of a nature usually associated with tuberculosis. Fifteen other calves were injected without ill effects. In 5 of these, the vole strain was recovered from tissues six months later; in 2, the organism was recovered after 564 and 544 days, respectively. Similar observations were made on rabbits and guinea pigs. The results indicate that the use of the vole acid-fast bacillus as a living vaccine is not unattended by risk. The authors believe that previous work indicating a low virulence was not carried out in a manner likely to determine the highest possible virulence.—*Virulence of a Strain of the Vole Acid-fast Bacillus (G 564)*, J. A. Young & J. S. Paterson, *Lancet*, May 24, 1947, 1: 707.—(A. G. Cohen)

Gastric Secretion in Tuberculosis.—In 100 patients with tuberculosis of the lungs fractional gastric determinations with test meals were conducted. About 28 per cent showed absence of free hydrochloric acid, and 47 per cent hypoacidity. Both anacidity and hypoacidity were more common among febrile

patients, in the more serious and bilateral cases and in the presence of high blood sedimentation rates. Roentgenoscopy in 53 patients failed to reveal any organic lesion of the stomach. In 8 cases marked signs of gastric atony were present. Age of patients or duration of the disease had little bearing on the result.—*Sobre la secreción gástrica y el tuberculoso pulmonar*, G. A. Guíroy, *Pub. del Centro de Investig. Tisiol.*, 1946, 10: 203.—(A. A. Moll)

Reticulocyte Rates.—Reticulocyte and red cell counts were made in 102 patients (54 men and 48 women) with pulmonary tuberculosis. As a basis for comparison similar determinations were conducted in a group of normal persons. The rates in patients varied according to the clinical type and the stage of the process, and even in the same case as changes in condition occurred. The absolute rate (number of reticulocytes) was not a reliable sign, but the relative rate (ratio to red cells) proved significant as evidence of the functional status of the bone marrow. Reticulocyte rates have no diagnostic value but they possess a certain prognostic significance and may help to determine the outcome and guide treatment. When the course was favorable the rate at first rose but decreased when improvement became definite. In stationary cases values were normal or increased. In unfavorable cases they were invariably above normal. All determinations were made during fasting periods. The results generally agreed with those reported by others, but values were lower in this series. A review of the literature on reticulocyte rates both in tuberculosis and other conditions is given. Normal figures taken for comparison were: men, red cells 4,500,000 to 5,000,000; women, 36,230, respectively. Reticulocyte ratio to red cells, 0.72 per cent for men and 0.79 per cent for women.—*El reticulocito en la tuberculosis pulmonar*, D. Raúl Rinaldi, *Pub. del Centro de Investig. Tisiol.*, 1946, 10: 125.—(A. A. Moll)

Congenital Absence of Lung.—A case is reported in which aplasia of the lung was associated with a rudimentary bronchus. The roentgenological findings in aplasia of the lung include displacement of the mediastinum to the affected side, opaque hemithorax and herniation of the opposite lung. Bronchograms show absence of the carina or a rudimentary bronchus, if present, as in the reported case.—*Congenital Aplasia of the Lung*, W. M. Nesbit, L. W. Paul & W. S. Middleton, *Am. J. Roentgenol.*, April, 1947, 57: 446.—(J. E. Farber)

Bronchiectasis, Nasal Polyps and Situs Inversus.—Bronchiectasis and nasal polyps occur in 10 per cent of persons with situs inversus. The hereditary mechanism in these conditions is dominant. There is a constitutional relation between lesions of the accessory sinuses and the bronchial tract. *Situs inversus* is a complication in development due to different genes including genes causing bronchiectasis and allergy.—*Transposition of Viscera, Bronchiectasis and Nasal Polyps*, J. Torgersen, *Acta radiol.*, 1947, 28: 17.—(J. E. Farber)

Asbestosis in Finland.—Asbestosis is an industrial disease not often observed in Scandinavia. In Finland, where a considerable asbestos industry has been established, the disease appears to occur to an appreciable extent. One hundred twenty-six cases of mild, moderate and far advanced stages of asbestosis are reported. The roentgenological characteristics of the changes in the lungs, the differential diagnosis, the classification in different stages and the importance of the time of exposure are discussed in detail.—*Changes in the Lungs in 126 Cases of Asbestosis Observed in Finland*, C. Wegelius, *Acta radiol.*, 1947, 28: 189.—(J. E. Farber)

Alumina Abrasives.—The authors describe an unusual form of lung disease apparently related to work in an industry previously

considered innocuous. As a preliminary step in the manufacture of corundum, all persons worked at the electric furnace processing a mixture of bauxite, iron and coke, for periods of several years. During this operation, dense white fumes, containing considerable quantities of alumina and silica in a fine state of division, are evolved. Of 344 exposed individuals, 35 manifested definite X-ray changes consisting of mediastinal widening and bilateral granular shadows becoming coarser in the more advanced cases. Emphysema was frequently present. There were 13 men with doubtful pulmonary changes. The main symptoms were cough and dyspnea; the latter was progressive in the severe cases, occasionally resulting in serious disability. Spontaneous pneumothorax, occasionally bilateral, was a frequent complication. Seven patients died of the disease. Pathologically, the disease is an interstitial lung fibrosis, non-nodular in type, and accompanied by severe emphysema. There was no evidence of tuberculosis in any of the specimens. The etiology is not clear; these workers were exposed not only to alumina and silica but also to small quantities of many other substances. These patients first came to notice in 1942; the authors believe that the disease developed as the result of increased exposure resulting from accelerated war production.—*Lung Changes Associated with the Manufacture of Alumina Abrasives*, C. G. Shaver & A. R. Riddell, *J. Indust. Hyg. & Toxicol.*, May, 1947, 21: 146.—(H. R. Nayer)

Early Coccidioidomycosis.—Due to a number of factors, it is probable that there will be a decided increase in the number of sporadic cases of coccidioid infections. Since serial roentgenograms in many cases are necessary for a detailed roentgen study of the disease, such a study was undertaken in an area where the disease was endemic. The résumé included complete immunological and laboratory studies and detailed residence and travel records. Working where the disease is prevalent, there is little difficulty in recognizing the disease, but it should be suspected in

any person with respiratory disease recently returning from an area of endemic infections. An intracutaneous test will rule out the disease in all but a few cases. Clinically it is most likely confused with influenza or bronchopneumonia. Roentgen findings in the early stages are nonspecific and could be explained by bronchopneumonia, tuberculosis, primary atypical pneumonia or rheumatic pneumonitis, especially the last two. The diagnosis in such cases can be made only on specific laboratory tests. With persistence of the infection hemoptysis with or without cavitation may occur and a diagnosis of tuberculosis made. Since the disease tends to clear in two to six weeks, the diagnosis is usually not difficult. However, over 21 cases were seen in whom the infection persisted from three to over twenty-four months. Diagnosis is especially difficult in the protracted type of the infection, having the roentgen appearance of advanced ulcerative tuberculosis. Mediastinal adenopathy accompanied many of the more severe cases or protracted infections, in which the disease may be confused with mediastinal neoplasm. Cases in which mediastinal adenopathy is dominant give rise to most of the fatalities and may be confused with Hodgkin's disease, tuberculosis, sarcoidosis or bronchiogenic carcinoma. Due to the type of onset the roentgenologist often sees residual "burned-out" foci, one or more circumscribed nodules 1 to 4 cm. in diameter or cyst-like foci easily confused with tuberculosis or metastasis. In cases having multiple residual nodules the onset is usually with severe constitutional symptoms and temperature of 100° to 103° F. for two to four weeks. The discrepancy between the clinical and roentgen findings is often helpful in establishing a diagnosis.—*Roentgen Findings in Early Coccidioidomycosis*, H. W. Jamison & R. A. Carter, *Radiology*, April, 1947, 48: 523.—(G. F. Mitchell)

Iron Lung in Whooping Cough.—The results obtained with the iron lung in spastic bronchitis encouraged the writers to try this

method in pertussis cases during the 1943 epidemic in Buenos Aires. Over 100 cases have been so treated, 53 which completed the treatment having been taken for this report. All were benefited. In some improvement was noticeable from the first application. Among outstanding results were the improved appetite and sleep, decrease of attacks and maintenance of weight in an appreciable number of cases. The iron lung might perhaps also prove useful to prevent bronchitis in pertussis. The number of applications reached as many as 20, being given on alternate days. The stay in the lung averaged twenty minutes and was invariably well tolerated. It is advisable to give the treatment on an empty stomach.—*La tos convulsa: Su tratamiento por el pulmón de acero*, R. Rabanague-Caballero & J. Dupont, *Pub. del Centro de Investig. Tisiol.*, 1946, 10: 25.—(A. A. Moll)

Sputum in Kerosene Poisoning.—By mistake, 2 patients treated for pulmonary tuberculosis received slow intravenous injections, 10 cc. and 4.5 cc., respectively, of kerosene. The sputa were examined for nine consecutive days. From these examinations it was found that the broncho-alveolar changes went through three different stages: (1) hypersecretion of mucus; (2) exudation with extravasation of leucocytes and macrophages; (3) reappearance of mucus hypersecretion which slowly disappeared on the ninth or tenth day. A fine emulsion of kerosene was found in the sputum even after several weeks. The reaction to the kerosene was an acute broncho-alveolitis as it is caused by other foreign bodies, but aggravated by its toxicity.—*La inclusion de esputos en dos casos clinicos de inyeccion intravenosa accidental de kerosene*, J. J. Scandroglio, *Hoja tisiol.*, March, 1946, 6: 21.—(W. Swienty)

Pancoast Tumors.—Symptoms and signs of Pancoast tumor are: (1) shoulder pain, which may be an early symptom; (2) damage to the brachial plexus, resulting in atrophy of arm and hand muscles; (3) Horner's syndrome;

(4) bone destruction, the paravertebral parts of the ribs being affected most commonly. Two cases of Pancoast tumors are presented; on autopsy squamous cell carcinomata were found.—*Beitrag zur Klinik der Geschwülste der oberen Lungenfurche (Pancoast-Tumoren)*, H. Schnetz & R. Salis, *Wien. klin. Wchnschr.*, February 14, 1947, 51: 89.—(G. C. Leiner)

Bronchogenic Carcinoma.—The symptoms, physical findings, diagnostic and therapeutic procedures of bronchogenic carcinoma are discussed. The importance of adequate pre- and postoperative management is stressed. Over a period of four years, 196 cases of bronchogenic carcinoma were seen. Of these, only 20 per cent were operable. The operative mortality was 5 per cent.—*Surgical Aspects of Bronchogenic Carcinoma*, J. C. Jones, *J. A. M. A.*, May 10, 1947, 134: 118.—(H. Abeles)

Primary Carcinoma of Lung.—Primary bronchogenic carcinoma is frequently confused with pulmonary tuberculosis. To help differentiate these two conditions the authors recommend the use of body section roentgenography in addition to the conventional diagnostic methods.—*Primary Bronchogenic Cancer Mistakenly Diagnosed as Pulmonary Tuberculosis*, W. R. Oechsli & K. B. Olson, *Am. J. Roentgenol.*, April, 1947, 57: 429.—(J. E. Farber)

Pulmonary Cysts.—Pulmonary cysts are divided into two chief types: those from the bronchial tree and those that are alveolar in origin. This article is concerned primarily with the bronchogenic type. Pulmonary cysts may be acquired or congenital. Fifty-four cases are included here and divided into three groups. The first group consisted of proved bronchogenic cysts, the second of cysts with fibrous walls probably bronchogenic with changes in wall due to pressure or infection, and the third of cystic bronchiectasis with dilatations greater than 3 cc. Twenty-four males and 20 females ranging in age from

7 to 58 with an average of 30. Cysts were found in all lobes of both lungs. Symptoms are characterized by their variability. The status of the bronchial communication and infection are the major factors in symptom production with cough and sputum being most common. Hemoptysis of varying amounts, dyspnea and pain are common. Mistakes in diagnosis are most often pneumonia and tuberculosis. Pulmonary suppurative disease may coexist and be primarily responsible for the patient's symptoms. Carcinoma may develop secondarily in bronchogenic cysts. Cystic bronchiectasis may be a factor in cyst production. X-ray is the most important single aid to diagnosis, but correlation with clinical history will most often give the correct diagnosis. Bronchoscopy and bronchography are seldom of positive value. If there is doubt as to diagnosis, exploratory thoracotomy is highly recommended. Recommended treatment is complete surgical removal.—*Pulmonary Cysts*, H. J. Moersch & O. T. Clagett, *J. Thoracic Surg.*, April, 1947, 16: 179.—(J. H. Cope)

Asthma in Children.—Thirty-four children from 2 to 14 years of age with recurrent attacks of asthma and nasopharyngeal lymphoid hyperplasia received radon treatment. The treatment was preceded by complete otolaryngologic, allergic and pediatric examinations. The treatment of each child consisted of two gram minutes of radon to each side of the nasopharynx once each month for an average of four treatments. In 23 of the 34 cases the lymphoid tissue disappeared completely. In some cases severe asthmatic attacks developed after the first or second treatment. All forms of asthma were represented. Sixty-eight per cent of the patients obtained from total to 50 per cent relief and 32 per cent obtained no relief.—*Asthma in Children: Treatment with the Radium Nasopharyngeal Applicator*, A. T. Ward, Jr., S. Livingston & D. A. Moffat, *J. A. M. A.*, April 12, 1947, 133: 1060.—(H. Abeles)

Obstructive Emphysema.—A fatal case of obstructive emphysema was observed in a 73-year-old female patient. Two years prior to her death, the patient had been operated on for a round cell sarcoma of the thyroid. Obstructive emphysema was caused by the later development of mediastinal metastases, which compressed both main bronchi, principally the right. A valvular effect was produced with persistent overinflation of both lungs, especially the right upper and middle lobes. Pressure readings from the right lung showed positive values during inspiration and expiration. Following lung puncture, the sites did not close, and extensive subcutaneous emphysema persisted until death a few days later. At autopsy the presence of extensive mediastinal metastases encasing the main bronchi was confirmed.—*Dyspnoe, positive Druckwerte der Lunge*, B. Zeerleder, *Schweiz. med. Wchnschr.*, December 21, 1946, 76: 1818.—(H. Marcus)

Pulmonary Embolism.—The prophylaxis of pulmonary embolism consists of the prevention of thrombus formation in the deep veins of the legs. The use of dicumerol offers the best method of protection in the age group between 40 and 65. In patients beyond the age of 65 interruption of the superficial femoral veins is the method of choice. Below the age of 40 the routine use of prophylactic measures is not advocated. If thrombosis has developed, interruption of the deep vein should be performed. If thrombophlebitis is present the treatment will consist of procaine block of the lumbar sympathetic nerves, heat application, heat and activity. Phlebotomy and thrombectomy will shorten the course of thrombophlebitis when combined with interruption of the superficial femoral vein. If infarcts continue after vein ligation, anticoagulents should be used.—*Venous Thrombosis and Pulmonary Embolism*, A. W. Allen, R. R. Linton & G. A. Donaldson, *J. A. M. A.*, April 26, 1947, 133: 1268.—(H. Abeles)

Pulmonary Decortication.—Results of modern decortication have been markedly influ-

enced by present methods of anesthesia, chemotherapy and blood transfusions. Timing is important in this operation, being best done in three to five weeks in uninfected cases, and from two to three weeks in infected cases. The visceral peel is removed to the parietal reflection; this is not removed as it prolongs the operation and increases shock without appreciable benefit. Two and sometimes three intercostal water-seal drains are used, for pulmonary reëxpansion; one in the first interspace anteriorly, and the second dependent in the postero-axillary line. Penicillin and transfusions are used routinely. The indications for decortication are uninfected, organizing hemothorax, infected organizing hemothorax, post-traumatic empyema. No operative deaths occurred in 125 patients. The operation may be done without rib resection. This operation is a major one and should not be done unless the hematocrit and serum protein levels are normal; plenty of blood for transfusion is available; chemotherapy should be used routinely before and after surgery and the services of a good anesthesiologist are mandatory.—*Total Pulmonary Decortication*, P. C. Samson & T. H. Burford, *J. Thoracic Surg.*, April, 1947, 16: 127.—(J. H. Cope)

Pulmonary Decortication.—Hemothorax is the most common complication of intrathoracic wounding, and up to the recent war there was diversity of treatment. The first decortication in the military services was done in 1943. This paper discusses 140 cases with organizing hemothoraces treated by decortication. Eighty-nine were uninfected and 51 were infected. There were no deaths. In 108 cases good results were obtained. In the remaining 32 cases, or 23 per cent, fair results were obtained in 26, and poor results in 6. Of 51 cases of preoperative empyema, 25 cases, or 50 per cent, healed primarily; 23 healed in a period of weeks, and 3 became chronic empyemata. The incidence of intrapleural clotting is higher in war than in wounds of civil life. At time of decortication, the peel removed was found to contain bacteria in

90 per cent of cases. At surgery, only the visceral peel was removed. It was considered very important to free all adhesion to the entire lung including the diaphragmatic surface, and also arrange the lobes in their normal position to secure rapid and complete reëxpansion.—*The Treatment of Organizing Hemothorax by Pulmonary Decortication*, W. M. Tuttle, H. T. Langston & R. T. Crowley, *J. Thoracic Surg.*, April, 1947, 16: 117.—(J. H. Cope)

Hemothorax and Empyema.—Two hundred and twenty-nine patients with fluid in the pleural space or drained empyemata are the subject of this review. Intrapleural foreign bodies, and the severity of the wounds, particularly abdomino-thoracic wounds are stressed as important etiological factors in empyemata. Simple hemothorax was treated by repeated aspirations without air replacement. Clotted hemothorax is diagnosed by aspiration of amounts of fluid from the pleural space that are smaller than physical and X-ray signs indicate. Efforts to attain cure by aspiration and breathing exercises are made. With large clotted hemothoraces, thoracotomy is used, with decortication of the scar being done. It is very important to free the lung completely. The scar tissue is removed from the thoracic wall to facilitate normal function. Small bronchopleural fistula that are opened are usually of no consequence when the chest is drained properly. Two drains, one high anterior and one postero-lateral, were used continually under water seal. If the lung did not expand completely, secondary decortication was done. In one case microscopic tubercles and acid-fast bacilli were found in the decorticated material. No lung lesion was found. Recovery was uneventful. Empyemata were treated with open drainage. No empyema was successfully treated with aspiration alone. Breathing exercises and early activity are essential to cure. Some previously treated empyemata need small unroofing operations to complete the cure. Bronchopleural fistulae usually closed when drainage was adequate. Decortication opera-

tions were the treatment of choice in infected hemothoraces unless the patient's condition was too poor or the hemothorax was less than 500 cc. The indications for decortication in empyema were large multilocular empyemata, depression of the lung apex, intrathoracic foreign bodies and failure of open drainage. The technique was the same as for clotted hemothorax. Penicillin is advisable prior to and after decortication. However, in this series the frequent occurrence of gram-negative non-penicillin sensitive organisms was noted. Breathing exercises are stressed as an essential part of treatment to promote lung expansions and cure.—*Hemothorax and Empyema in a Thoracic Center, G. N. J. Sommer, Jr. & W. O. Mills, J. Thoracic Surg., April, 1947, 16: 154.*—(J. H. Cope)

Chronic Hemothorax.—Chronic traumatic pneumothorax is defined as a hemothorax that is not reducible by thoracocentesis, even though fresh blood has ceased to enter the pleural cavity. Even though the complete explanation of organizing hemothorax cannot be given, the process as seen clinically can be accounted for by the deposit of fibrin on the pleural surfaces. The basic response of pleura to the irritating factors of trauma or blood is serous effusion. Severity or type of trauma, with or without bacteria, may result in excess fibrin. A clotted hemothorax or a fibrinothorax becomes a fibrothorax, by organization of the intrapleural mass, similar to vascular clots. The different clinical behavior and manifestations in infected patients is explained by fibrin acting as a barrier to leucocytic invasion, resulting in a latent period before the centre of the pleural mass is reached, with the formation of pus. Infolded lung is explained as an entity that can be confused with gross, organizing hemothorax, but is recognizable on lateral X-ray film as a more patchy and diffuse process, with no localization. The importance of recognizing the condition, particularly at time of decortication, is stressed, as adhesions between lobes and portions of the lung upon itself must be separated to allow for complete and rapid

reexpansion. However, lung-infolding alone may be confused with organizing hemothorax. It is important to recognize this entity, and while reexpansion may be slow, surgery is not necessary.—*The Pathology of Chronic Traumatic Hemothorax, H. T. Langston & W. M. Tuttle, J. Thoracic Surg., April, 1947, 16: 99.*—(J. H. Cope)

Diaphragmatic Hernia Repair.—This is an experimental study in the use of a sliding fibro-voluntary muscle flap in the repair of diaphragmatic hernia. Dogs were used for the study. A large portion of the left diaphragm was excised in each dog. The original chest incision was over the tenth rib. The *latissimus dorsi* was incised over the upper border of the tenth and reflected down to below the eleventh rib as a pedicle. The eleventh rib was resected subperiosteally. The pleura was incised through the bed of the eleventh rib. The *latissimus* pedicle was swung into the pleural space and sutured over the diaphragmatic defect without tension. The cephalad portion of the *latissimus* was sutured to the tenth intercostal substance and both were sutured to the caudal pedicle of the *latissimus* where it crossed the cut edge of the bed of the eleventh rib, thus reestablishing a normal *latissimus* function. Postoperatively no significant deformity was noted. Subsequent follow-up showed a flattened left diaphragm. Though displacement of the esophageal hiatus occurred, no hernias were detected. Sections of *latissimus* showed fatty degeneration and replacement fibrosis in five months.—*Transsthoracic Repair of Large Diaphragmatic Hernias: An Experimental Study, T. C. Chisholm, J. Thoracic Surg., April, 1947, 16: 200.*—(J. H. Cope)

Early Sarcoidosis.—In an attempt to determine whether there are any lesions suggestive or characteristic of early pulmonary sarcoid disease, a series of cases were studied. While sarcoidosis, a disease of protean manifestations, is often seen when only one system is involved, pulmonary involvement is seen at some time in 90 per cent of cases. Roentgen

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findings are also protean in character. While many writers have described the various pulmonary findings, only a few have mentioned what they believe to be a characteristic early lesion; of these most believe that the diffuse miliary type is probably the early lesion. Absolutely nothing characteristic was noted in the findings of the individual case in the series reviewed. However, the intrathoracic adenopathy did tend to conform to a curious pattern in half of the cases revealing simultaneous enlargement of both sets of hilar nodes and only the right upper paratracheal nodes. The writer believes that the roentgen findings may be one of the four following types: (1) disseminated miliary parenchymal lesions, (2) diffuse or localized nodular parenchymal lesions, (3) parenchymal densities with hilar and paratracheal adenopathy or (4) hilar and paratracheal adenopathy alone. The miliary type of pulmonary sarcoidosis occurred as an early finding in only a few of the cases.—*Pulmonary Sarcoidosis: The Early Roentgen Findings*, L. H. Garland, *Radiology*, April, 1947, 48: 333.—(G. F. Mitchell)

Sarcoidosis Simulating Glomerulonephritis.—Sarcoidosis is now recognized as a generalized granulomatous disease of unknown cause which may involve any part of the body. Renal involvement, however, especially when accompanied by extensive retinal changes, is so unusual in sarcoidosis that a case of this type is reported in detail.

A 23-year-old Negro developed nocturia in December, 1944; weight loss, headaches and visual impairment gradually appeared. In April, 1945, fever, retinitis, anemia, albuminuria and azotemia with normal blood pressure were found. In June, enlarged lymph nodes were biopsied and showed sarcoidosis. Hypercalcemia and hyperglobulinemia and insensitivity to tuberculin were present. During the next ten months fever, lymphadenopathy and retinal changes subsided; hypercalcemia decreased; anemia and renal insufficiency improved. Only 3 other cases of sarcoidosis with renal insufficiency could be discovered in the literature. These 3 presented symptoms quite similar to the authors' case. The pertinent data in all 4 cases are presented in tabular form. In the typical of those found in nephritis. The arteries were little if at all involved; the veins completely bore the brunt of the pathological changes; and the retinal changes subsided while the renal insufficiency did not improve, which indicates that the retinitis was not due to renal failure. While the diagnosis of sarcoidosis can be made with certainty only on finding the typical pathological changes, the disease should be suspected when hyperglobulinemia and hypercalcemia are found in the presence of azotemia. (Illustrated)—*Sarcoidosis Simulating Glomerulonephritis*, H. F. Klinefelter & S. M. Salley, *Bull. Johns Hopkins Hosp.*, November, 1946, 79: 333.—(J. S. Woolley)

CONSTITUTION OF CHEMOTHERAPEUTIC AGENTS IN EXPERIMENTAL TUBERCULOSIS^{1,2}

B. L. FREEDLANDER AND F. A. FRENCH

The history of chemotherapy represents the gradual evolution of the rational over that of the empirical approach. A brief historical review will illustrate this.

The prevailing concept of the pre-Ehrlich period (1870-1900) was that of chemical sterilization of the body, without any thought being given to toxic effects of the drugs. Such chemicals as bichloride of mercury and phenol were used systemically, with disastrous results to the host. No significant chemotherapy on tuberculosis was done during this period.

The Ehrlich period (1900-1920) introduced the idea of specific antimicrobial chemotherapy, which attempted to develop drugs which were more toxic to the parasite than to the host. It is interesting that it was some forty years later that Ehrlich's so-called "drug-receptors" were identified with bacterial enzymes. Relative to tuberculosis chemotherapeutic research was largely confined to the dyes. It was shown that certain dyes, such as acridine orange and methylene blue, penetrated to the centre of tubercles, but were without significant therapeutic effect in animals.

The research work of the period 1920-1935 was essentially empirical and unfruitful of results, and is more to be remembered for the magnitude of the tremendous number of agents tried than for the introduction of any new concepts. These drugs included the heavy metals, particularly gold, copper, mercury and arsenic; also the chaulmoogrates and hundreds of dyes. Perhaps the chemotherapy of the heavy metals should be regarded as having contributed the concept that drugs may act indirectly through stimulation of the immune forces of the host by way of the reticulo-endothelial system.

The sulfonamide era (1935-1945) marked the beginning of modern rational chemotherapy. Sulfonanilamide and its derivatives were of negligible activity in experimental tuberculosis; however, their discovery introduced the concept of therapeutic agents acting through competition for essential metabolites. Although more than a hundred sulfones, including promin and diasone, have been tested in experimental tuberculosis, they are, on the whole, too toxic for humans; and, while some of the derivatives have relatively lower toxicity, they do not enhance the activity of the parent compound, diaminodiphenylsulfone. The main contribution of the sulfones to chemotherapy was the introduction of the concept that non-acid-dissociating compounds, such as the sulfones, permeate the tubercle bacillus more readily than the acid-dissociating sulfonamides.

The discovery of antibiotics opened a large new field. Already hundreds of

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² From the Harold Brunn Research Institute, Mt. Zion Hospital, San Francisco.

antibiotics have been prepared, and several have been reported to have some effect on experimental tuberculosis. Streptomycin will be discussed by subsequent speakers. Other antibiotics reported to have a favorable effect on tuberculosis include subtilin and new antibiotics from fungi and lichens. With the exception of streptomycin, critical animal therapeutic tests have not been performed on them.

Several new synthetic chemicals have been reported for use in experimental tuberculosis during the past five years. These include p-aminosalicylic acid; 5-amino-2-butoxypyridine; 1,1,1-trichloro-2,2-bis(p-aminophenyl)-ethane;

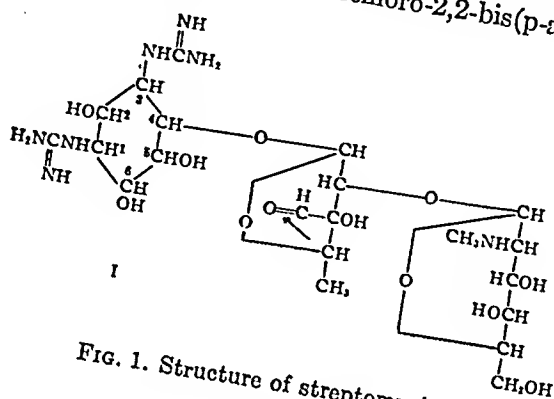


Fig. 1. Structure of streptomycin

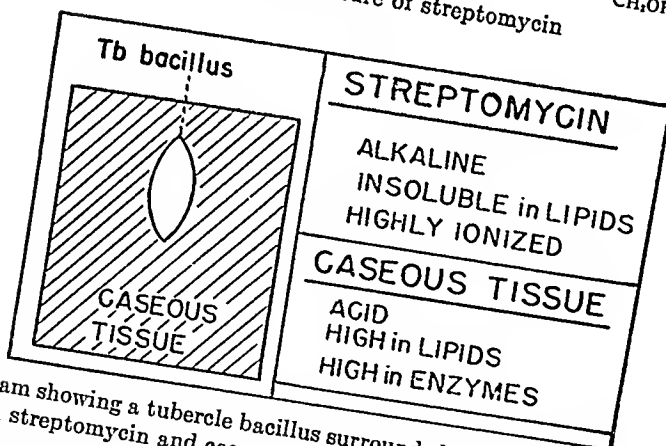


Fig. 2. Diagram showing a tubercle bacillus surrounded by caseous matter and chemical relation between streptomycin and caseous tissue.

phenothiazines; 9-aminoacridine derivatives; iodonium derivatives; benzophenones and other ketones. Much of the experimental work on para-aminosalicylic acid was done abroad; it appears to be a promising compound, both *in vitro* and *in vivo*, and is of very low toxicity. The compound, 5-amino-2-butoxypyridine, reported by Feinstone, is bacteriostatic in very high dilution; animal experiments have not as yet been reported. The compound 1,1,1-trichloro-2,2-bis(p-aminophenyl)-ethane is related to DDT and shows some therapeutic effect in animal tuberculosis. The compounds phenothiazines, 9-aminoacridine derivatives, iodonium derivatives and benzophenones have a

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high *in vitro* effect, but so far are without therapeutic action in animals. It is of interest that so many compounds of unrelated structure are bacteriostatic. This would justify optimism that more successful clinical therapeutic agents will ultimately be found.

Another new field of chemotherapy has been opened by structural chemical alterations of essential metabolites, vitamins and antibiotics. We can now deliberately make a slight chemical alteration in these biological agents. Figure 1 shows the structure of streptomycin. Note the highly basic guanidine groups, and also the aldehyde group (with the arrow pointing to it). This aldehyde group has been reduced catalytically in several laboratories, to form dihydrostreptomycin, which is more stable than streptomycin, and is just as bacteriostatic *in vitro*. In our laboratories we have found its therapeutic effect in guinea pigs to be fully, if not more effective than streptomycin. It is possible that dihydrostreptomycin may be more favorably absorbed or distributed in the blood and tissues than the original streptomycin.

Streptomycin seems to be clinically more effective in early productive and exudative lesions, which have not yet caseated. This suggests that streptomycin might have difficulty in crossing the caseous barrier surrounding the tubercle bacillus. Figure 2 diagrammatically illustrates this barrier. Streptomycin is highly basic, highly water soluble and highly ionized. Caseous tissue is slightly acid and is high in lipids and enzymes. These properties might constitute a barrier which prevents streptomycin from reaching the tubercle bacillus in sufficient concentration. The subsequent speakers will, I think, give clinical evidence to substantiate this theory. Streptomycin is clinically relatively ineffective in those forms of chronic pulmonary tuberculosis wherein caseation predominates. It is effective in early tuberculous pneumonia if reagent, but not in older caseous areas. Streptomycin is ineffective in empyema, which are usually acid in reaction, and also in brain lesions, which organ has a high lipid content. It is effective in large caseous lymph nodes only after drainage has taken place.

These concepts of chemotherapy constitute a long step from the empiricism of a few decades ago.

TEST TUBE EVALUATION OF TUBERCULOSTATIC AGENTS¹

GUY P. YOUMANS²

The testing of tuberculostatic agents *in vitro* involves the recognition of certain principles which are derived from the nature of the substances being tested and the nature of the tubercle bacillus. Since the bacteriostatic action of many agents is inhibited or reversed by organic materials, a simple chemically defined medium should be employed. In such a medium the synthetic metabolic activities of the tubercle bacilli are fully employed and consequently bacteriostasis by added substances is favored. Addition of growth stimulating or inhibitory agents to the basic medium should be avoided since, on the one hand, slight bacteriostasis of a compound may be obscured and, on the other, synergistic action may serve to make a weakly bacteriostatic agent appear highly active.

Only virulent human type tubercle bacilli should be used as test organisms and, because of the inverse relationship between the number of bacteria and the bacteriostatic power of many substances, a uniform and not too large inoculum of tubercle bacilli should be used. A serial dilution technique, using a modified Proskauer and Beck medium and subsurface (deep seated or submerged) growth of virulent tubercle bacilli, provides a fairly accurate and rapid test method. The test can be modified so as to determine the bacteriostatic activity of substances under a variety of conditions, and can also be used to assess the relative susceptibility of strains of tubercle bacilli to a given growth-inhibiting agent. If an agent, such as streptomycin, is not affected by the presence of protein, more rapid growth of the tubercle bacilli can be obtained by the addition of plasma, serum or purified albumin.

Results obtained from the testing of over three thousand chemical compounds including many antibiotics show that *in vitro* tests for bacteriostatic activity are of great value for the elimination of inactive substances. *In vivo* activity, however, cannot be predicted from *in vitro* bacteriostatic activity.

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² Northwestern University Medical School, 303 East Chicago Ave., Chicago 11, Illinois.

CHEMOTHERAPEUTIC TESTING IN EXPERIMENTAL TUBERCULOSIS^{1,2}

M. I. SMITH

Prior to 1940, when practically all attempts at chemotherapy in experimental tuberculosis led to little more than negative results and disappointments, the problem of selecting adequate methods for chemotherapeutic testing had no more than an academic interest. The use of the classical guinea pig as the test object was the accepted procedure, though much dissatisfaction prevailed among workers in this field on account of its extraordinary susceptibility to tuberculous infection. It was argued that the disease is so overwhelming in the guinea pig that scarcely any drug, even if effective in more resistant species, could have a perceptibly salutary effect in this animal. Hence the suggestion that a more chronic and less virulent type of experimental infection be employed for chemotherapeutic evaluation such as, for example, the chronic pulmonary miliary tuberculosis in rabbits produced by intravenous injection of a human strain of tubercle bacilli, or the chronic, more or less localized tuberculous orchitis in rabbits resulting from the intratesticular injection of tubercle bacilli of a human strain.

With the advent of the sulfones and more recently of the antibiotic streptomycin, substances of proved chemotherapeutic efficacy even in the highly susceptible guinea pig, new leads have been uncovered and the whole subject of chemotherapy in tuberculosis has taken on a different and greatly accelerated tempo. The promising results achieved in recent years with the newer chemotherapeutic agents have made it desirable or even necessary to resort to test objects other than the classical guinea pig, not only for the purpose of saving time and material but also for the purpose of better elucidation of obscure mechanisms through the use of new techniques. Other methods of testing chemotherapeutic agents will thus be coming into use and we may properly inquire into their adequacy and the rôle which they are likely to play in furthering the development of new chemotherapeutic agents.

Time will not permit much more than to enumerate the methods which have been used from time to time, to describe them as briefly as possible and to indicate their advantages or disadvantages and what may be expected of them.

For convenience the various methods may be arranged in the following order.

(1) Tuberculous orchitis in the rabbit, produced by the intratesticular injection of a large dose, about 5 mg., of tubercle bacilli, human strain H37 (1). Characteristic localized lesions develop usually in two to four weeks. The effects of treatment, local or systemic, can be followed by mere inspection or by measuring the lesions or by examination of stained smears from the lesions. The

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² From the Division of Physiology, National Institute of Health, Bethesda, Maryland.

localized nature of the lesions also permits studies on the comparative distribution of chemotherapeutic agents as between tuberculous and normal tissue (in this instance the inoculated tuberculous testicle as contrasted with the non-inoculated normal testicle) in the same animal. The method was first described and used in 1922. It has not been employed in connection with the newer and more effective chemotherapeutic agents.

(2) Systemic infection in rabbits by the intravenous injection of an avian strain of tubercle bacilli which produces a rapidly fatal infection characterized by rapid proliferation of tubercle bacilli in the lung tissues (2, 3). Suffice it to say that the first intimation of the chemotherapeutic efficacy of *p,p'*-diaminodiphenylsulfone, the parent substance of many sulfone derivatives, came from the use of this method by Rist, Bloch and Hamon (2). Systemic infection in rabbits with virulent bovine tubercle bacilli has been treated with *N'*-dodecanoylsulfanilamide and sulfapyridine with negative results (4), with promin with only partially positive results (5). Positive results have also been reported in the treatment with promin in cutaneous tuberculosis in rabbits induced by intracutaneous inoculation of virulent bovine tubercle bacilli (6).

(3) Experimental tuberculosis in the rat, predominantly pulmonary, results from the intraperitoneal or intravenous injection of rather large doses of human or bovine tubercle bacilli (7, 8, 9). The multiplying bacilli in the tissues of the rat provoke early and progressive proliferation of monocytes, foam cells, epithelioid cells and occasionally giant cells. These cellular aggregates, harboring great numbers of tubercle bacilli, may become so numerous in the lungs and so densely packed as to obliterate alveolar space and to interfere mechanically with the normal respiratory function. This lesion lacks the characteristic and typical architecture of the classical tubercle with the caseation necrosis and lymphocytic infiltration as seen in man and in susceptible animals. In general, it may be stated that the rat is extremely refractory to tuberculous infection, though an increased susceptibility has been reported in hypophysectomized rats (10) and in rats rendered hyperglycemic by experimental procedures (11). In our experience the rat is also refractory to the action of chemotherapeutic agents, since it has not been possible to check effectively the proliferation of tubercle bacilli in the tissues of the rat either with sulfones or with streptomycin. It should be emphasized, however, that by combined chemotherapy with streptomycin and the sulfone derivative, promin, it has been possible to sterilize about 50 per cent of the animals so treated (12).

(4) Mouse tuberculosis, also predominantly pulmonary, produced by a similar technique. It presents a histological picture of a character similar to if not identical with the tuberculous granuloma in rats (13). It was first used for chemotherapy by Thomas and Dessau in 1939, when negative results were reported with tuberculo-polysaccharide (14). In 1943 Nitti and Jouin reported lack of protection from *p*-aminobenzene sulfonamide in experimental miliary tuberculosis in the mouse (15) and in 1945 essentially negative results were reported from treatment with promin (16). More recently Youmans and associates (17) have employed this technique in chemotherapy studies with strepto-

mycin and reported a suppressive effect from large doses, 120,000 units per kg. per day. This method has the advantage of economy of space, economy of test material, and economy of time as shown in Youman's experiments where with proper technique the merits of a given chemotherapeutic agent can be evaluated in about one month. Critical study of the results reported by the various investigators who made use of this technique indicates that, like the rat, the infection in the mouse is refractory to the chemotherapeutic action of such drugs as have proved effective in retarding or suppressing the disease in the more susceptible guinea pig, all of which indicates that the biochemistry of tuberculosis in the refractory rat or mouse is fundamentally different from that of the susceptible guinea pig and this raises the very serious question of the ultimate value of these more economical tests.

In addition to the foregoing, brief mention should be made of the omental weight test in the guinea pig as suggested by Bernheim and associates (18); the appearance time of tubercle bacilli in the spleen of guinea pigs as described by Woodruff and associates (19); the chorio-allantoic membrane of the chick embryo screening test, first described by Emmart and the writer in 1941 (20), and later employed by Emmart in this laboratory (21, 22) and by McKee and Alure-Werber (23). Each of these may have its particular usefulness in exploratory work, though no one would advocate their exclusive use as a means of evaluating chemotherapeutic efficacy.

Several papers have been published on the susceptibility of the golden hamster (*Cricetus auratus*) to the tubercle bacillus (24, 25, 26, 27). The data are by no means in accord, and no systematic study has apparently been made to determine its possible usefulness as a test object in chemotherapeutic evaluation. Negative results have been reported recently with subtilin in this species (28) but the chemotherapeutic efficacy of this antibiotic in tuberculosis has not yet been determined.

CONCLUSIONS

Several of the better known methods for evaluation of antituberculosis activity have been briefly reviewed, their merits and disadvantages pointed out. In the writer's opinion any one of them if properly controlled may be used to advantage to evaluate antituberculosis activity of a new chemotherapeutic agent with reference to a suitable standard. Prior to the recognition of streptomycin, p,p'-diaminodiphenylsulfone or one of its derivatives, such as promin, was considered a suitable standard of reference (29). The greater potency of streptomycin and its relatively lower toxicity should hereafter make it the standard of choice. While any of the methods enumerated may be used to advantage in some particular problem it is believed that the classical guinea pig experiment will continue to maintain a key position as a routine test object in the search for more effective and less toxic antituberculosis chemotherapeutic agents. With the use of standard virulent strains of tubercle bacilli and a large infecting dose as previously described (29), the test period need not be longer than 60 to 100 days when a given experiment can be terminated and the value of a new chemo-

therapeutic agent pretty well ascertained. Data obtained under such an experimental set-up give, on the whole, more information, greater assurance and leave less uncertainty than with any of the other methods, thus fully justifying the greater expenditure of time and material inherent in the guinea pig test, as compared with some of the more economical methods referred to.

CONCLUSIONES

Comprobación Quimioterapéutica en la Tuberculosis Experimental

Al repasar sucintamente varias de las técnicas mejor conocidas para la justipreciar la actividad antituberculosa, señálanse sus méritos y desventajas. Opina el A. que cualquiera de ellas, debidamente fiscalizada, puede ser utilizada provechosamente para avaluar la actividad antituberculosa de un nuevo agente quimioterapéutico con referencia a una pauta adecuada. Antes de conocerse la estreptomycin, la p,p'-diaminodifenilsulfona, o uno de sus derivados, como la promina, estaba considerada como pauta adecuada de comparación (29). La potencia mayor de la estreptomycin y su toxicidad relativamente menor deben de ahora en adelante convertirla en pauta de elección. Aunque cualquiera de las técnicas enumeradas puede ser usada provechosamente en algún problema dado, parece que el clásico experimento en el cobayo continuará manteniendo su posición cardinal como ensayo sistemático en la busca de agentes quimioterapéuticos antituberculosos más eficaces y menos tóxicos. Empleando cepas virulentas tipos de bacilos tuberculosos y una gran dosis infectante según se ha descrito previamente (29), el período de comprobación no tiene que exceder de 60 a 100 días, para cuya fecha ya puede terminarse un experimento dado y averiguarse bastante bien el valor de un nuevo agente quimioterapéutico. Los datos obtenidos con un sistema experimental y mayor seguridad y dejan menos incertidumbre en conjunto más información y justificando así el mayor dispendio de tiempo y de ninguna de las otras técnicas, material inherente en la prueba del cobayo, comparada con algunas de las técnicas más económicas ya mencionadas.

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STREPTOMYCIN IN GUINEA PIG TUBERCULOSIS¹

W. STEENKEN, JR.²

Recently, Waksman and his coworkers reported the discovery of streptomycin, produced by *Actinomyces griseus*. This was found to be very active against the tubercle bacillus in the test tube and of such low toxicity as to be well tolerated by animals and man.

Feldman and Hinshaw, Youmans and McCarter, Smith, McClosky and Emmart, and ourselves have shown that streptomycin markedly retards the progression of tuberculosis in the experimental animal.

More recently, Smith, and also Bogen, have shown that a combination of streptomycin and promin, or some other derivative of diaminodiphenylsulfone, acts synergistically, and has a much more favorable effect upon experimental disease than either drug alone.

The effect of streptomycin on tuberculosis in guinea pigs is often dramatic. Many animals that had extensive disease are apparently cured as evidenced by: (1) normal appearing organs by gross inspection; (2) the absence of microscopic evidence of tuberculosis; (3) negative results on subinoculation of tissues from these treated pigs.

At present, it is not known how long streptomycin therapy should be continued in guinea pigs to effect a permanent cure. Likewise, it has not yet been determined what is the minimum dose of streptomycin necessary to cause a regression of an already progressive tuberculosis in guinea pigs. Feldman and Bogen and ourselves have shown the effect of treatment with varying maximum and minimum doses of streptomycin immediately after the animals have been infected with virulent tubercle bacilli. The results of these experiments show that equal effects from the drug were obtained within the range of 10,000 and 25,000 units per twenty-four hours, whether it was given once a day or several times a day, or whether 20,000 units were given once every other day. In our most recent experiment, however, we found that, if treatment was started when there was already an advanced disease of four weeks' duration, better results were obtained if the animals were treated with 18,000 units a day divided into four doses, than if the drug was given in a single daily dose of 10,000 units. This brings out the important fact that in animal experimentation one must take into account the extent and duration of the disease in determining the time intervals and the amount of the drug to be administered in order to obtain the maximum effect of streptomycin therapy.

In one experiment we injected 18,000 units of streptomycin per day (divided into four injections) into normal guinea pigs starting two days prior to inoculation with .001 mg. wet weight of H37 Rv tubercle bacilli. It was found that the

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² Research and Clinical Laboratory, Trudeau Sanatorium, Trudeau, New York.

STREPTOMYCIN IN TUBERCULOSIS

streptomycin in the animal body did not prevent the dissemination of the bacilli, nor the development of tuberculosis. However, streptomycin injections were continued and, with the development of tuberculin sensitivity, the disease retrogressed.

Since the appearance of resistance of tubercle bacilli to streptomycin in patients after a month or more of therapy occurs in a high percentage of the cases, it should be mentioned that this finding does not occur so constantly in guinea pigs, nor in so high a percentage, as it does in human beings. In fact, Karlson and Feldman are the only observers to date who have reported such findings, and they noted that it was only occasionally that an animal produced resistant forms after prolonged treatment with the drug. In our series, after 125 days of therapy, we were unable to recover any resistant forms, using the Tween 80 albumin liquid media for sensitivity tests.

TOXICITY OF STREPTOMYCIN^{1, 2}

(Abstract)

WALSH McDERMOTT AND CARL MUSCHENHEIM

Approximately 60 individuals with various forms of tuberculosis have been treated for long periods of time (two to four months) with a constant and highly purified preparation of streptomycin. The drug used was prepared from crystalline material and is estimated to be at least 95 per cent pure. The function of a number of organs and systems was tested prior to the administration of therapy and at periodic periods thereafter. Moreover, the patients were examined daily for evidence of toxicity. The incidence of toxemic reactions following the use of this highly purified material will be presented in detail as well as observations on the tissues of 6 patients who died during therapy.

¹ Presented before the Medical Section, as part of a symposium on *Antibiotics and Chemotherapy in Tuberculosis*, at the 43rd annual meeting of the National Tuberculosis Association, San Francisco, California, June 18, 1947.

² From the Department of Medicine, Cornell University Medical College, and the New York Hospital, New York, New York.

TECHNIQUE OF STREPTOMYCIN ADMINISTRATION¹

H. CORWIN HINSHAW² AND WILLIAM H. FELDMAN³

The effectiveness of streptomycin treatment in some types of tuberculosis has been demonstrated to the satisfaction of all participants in the coöperative project now under way under the auspices of the American Trudeau Society. The techniques of treatment were developed on an empirical basis and it remains to be determined whether these are the most effective, the least expensive and the most convenient methods of administering streptomycin. Methods may be developed which will reduce the incidence and severity of toxemic reactions, reduce the difficulties, discomfort and expense of administration; and possibly increase the effectiveness. But until improved methods have been developed, we can only recommend that the known effective methods of treatment with streptomycin be employed.

Most of the patients reported to you have received from 1.8 to 3 g. of streptomycin per twenty-four hours. This dose is in the effective range, but is also definitely in the toxic range. Sufficient experience has been developed with a dose of only 1 g. per day to indicate that this amount is adequate for the treatment of some types of tuberculosis, but possibly not for all of the types which respond to streptomycin. The dose of 1 g. per day is distinctly less toxic than the larger doses. Therefore, we would recommend that for an adult of average build the dose be 1 g. per day for the less critical types of tuberculous infection and 1.5 or possibly 2 g. per day for the most serious, critical types of tuberculosis. Should a dose of 3 g. per day be employed with commercial grades of streptomycin, more severe toxemic effects than reported by Doctor McDermott should be anticipated.

The interval between injections may be prolonged to at least six hours. Even less frequent injections may be employed later but until these dosages have been more completely studied they will not be recommended. The less frequent injections may not be equally effective, and the temporarily elevated blood levels may enhance the toxicity of streptomycin. In guinea pigs, it has been determined that injections may be given every twelve or even every twenty-four hours with results approximately as good as if injections are given more frequently.

Most of the observations reported to you have been made concerning patients who received treatment continuously for four months, but this may be longer than necessary.

In most patients predominantly drug-resistant strains of tubercle bacilli will have developed before four months have elapsed, but this is not true of all. It

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² Division of Medicine, Mayo Clinic, Rochester, Minnesota.

³ Division of Experimental Medicine, Mayo Foundation, Rochester, Minnesota.

is not known whether large or small doses accelerate or delay the rate of development of resistance to the drug. It cannot be determined by usual resistance tests whether only a few or all of the tubercle bacilli in a specimen are resistant.

The intermittent administration of streptomycin is now being used on a trial basis in our institution, and evidence indicates that some of the toxic potentialities of the drug may be avoided by such use. It has not been determined if the drug is equally effective when given in this manner.

Streptomycin is readily soluble and solutions may conveniently be made which contain from 200 to 250 mg. per cc. It is advocated that solutions be freshly made and refrigerated to discourage the growth of any microorganisms which may have accidentally contaminated the solution. Streptomycin solutions do not deteriorate in potency even at room temperature for several days or longer. There are no important advantages to either the sulfate or the hydrochloride salt.

The intramuscular route of administration is preferable, but it is not necessary to use large, long and dull needles. Manufacturers are steadily reducing the irritant properties of commercial streptomycin, and it may be that before long the subcutaneous route may be employed. Intravenous administration is not advocated because of reported instances of increased toxicity when the drug is administered by this route.

When tuberculous meningitis is treated with streptomycin, intrathecal use of the drug is necessary in addition to parenteral injections. The most highly purified preparations available should be utilized for this purpose. The usual dose is 50 to 100 mg. daily, diluted in 5 to 10 cc. of sterile saline or cerebrospinal fluid and introduced by gravity after withdrawal of 10 to 15 cc. of cerebrospinal fluid.

Streptomycin has also been administered as an aerosol, but there is some doubt that this offers any distinct advantage to the patient who is also receiving the drug parenterally. A daily dose of 0.5 g. dissolved in 20 cc. of saline and divided into 6 to 10 doses is suggested for aerosol use.

The use of streptomycin combined with other antibacterial agents cannot be recommended at the present time because studies now under way along this line are incomplete.

The use of local anesthetics, antihistamine drugs and substances to delay absorption cannot be recommended until greater experience has been reported.

In conclusion, we advise that under most conditions 1 or 2 g. of streptomycin be given per day in divided doses every six hours, intramuscularly for periods of three to four months.

EFFECT OF STREPTOMYCIN ON EARLY TUBERCULOUS PULMONARY LESIONS^{1, 2, 3}

A Preliminary Report

DANIEL E. JENKINS,⁴ WILLIAM M. PECK,⁵ J. J. ROWLAND REID⁶
AND HENRY STUART WILLIS⁷

This report of work still in progress is part of a very pleasant coöperative venture between the Maybury Sanatorium, Northville, Michigan and the University of Michigan Hospital at Ann Arbor, Michigan.

Such a combination of institutions has allowed us an unusual opportunity to obtain patients with recently acquired pulmonary tuberculosis, the duration of the disease having been accurately documented by a previous "negative" chest roentgenogram. In a few instances the recent spread of disease into a previously normal lobe or lung has been used for evaluation. No cases have been admitted to the study without bacteriological proof of the diagnosis.

A total of 45 patients has been included in this project. In order to provide some basis for the evaluation of results, the patients have been separated into two roughly comparable groups. One group of 23 patients received streptomycin intramuscularly in a dosage of 2.0 g. per day, in divided doses every four hours, for ninety days while on a specially supervised program of bed-rest. The other group of 22 patients received the same schedule of bed-rest but without the drug. Due to the great difficulty in obtaining strict controls in a disease such as tuberculosis, we have preferred to designate the latter group as a "parallel" rather than a control series.

The streptomycin group and the parallel series are comparable in the aspects shown in figure 1. There were 8 cases of far advanced disease, 12 of moderately advanced and 3 of minimal extent in the streptomycin series. The parallel group contained 5 far advanced, 16 moderately advanced and one minimal case. It should be emphasized that the majority of cases in this study had serious tuberculosis at the onset of treatment, and that the term "early tuberculosis" is in most

¹ Presented before the Medical Section, as part of a symposium on *Antibiotics and Chemotherapy in Tuberculosis*, at the 43rd annual meeting of the National Tuberculosis Association, San Francisco, California, June 18, 1947.

² The streptomycin for this study was provided by E. R. Squibb & Sons, New York, New York, through the American Trudeau Society.

³ This project has been aided by a grant from the Research Grants Division of the United States Public Health Service.

⁴ The Tuberculosis Unit, Department of Internal Medicine, University of Michigan School of Medicine, Ann Arbor, Michigan. Present address: Baylor University College of Medicine, Houston, Texas.

⁵ William H. Maybury Sanatorium (Detroit Municipal Tuberculosis Sanatorium), Northville, Michigan.

⁶ Chas. Pfizer Fellow in Antibiotics, University of Michigan, and the Tuberculosis Unit, Department of Internal Medicine, University of Michigan School of Medicine, Ann Arbor, Michigan.

⁷ Sanatorium, North Carolina.

instances not synonymous with "minimal tuberculosis" as far as this report is concerned.

To allow as objective an evaluation of the results as possible in a preliminary report, such as this, roentgenographic observations and bacteriological data have been chosen for presentation. In each case the roentgenographic changes rep-

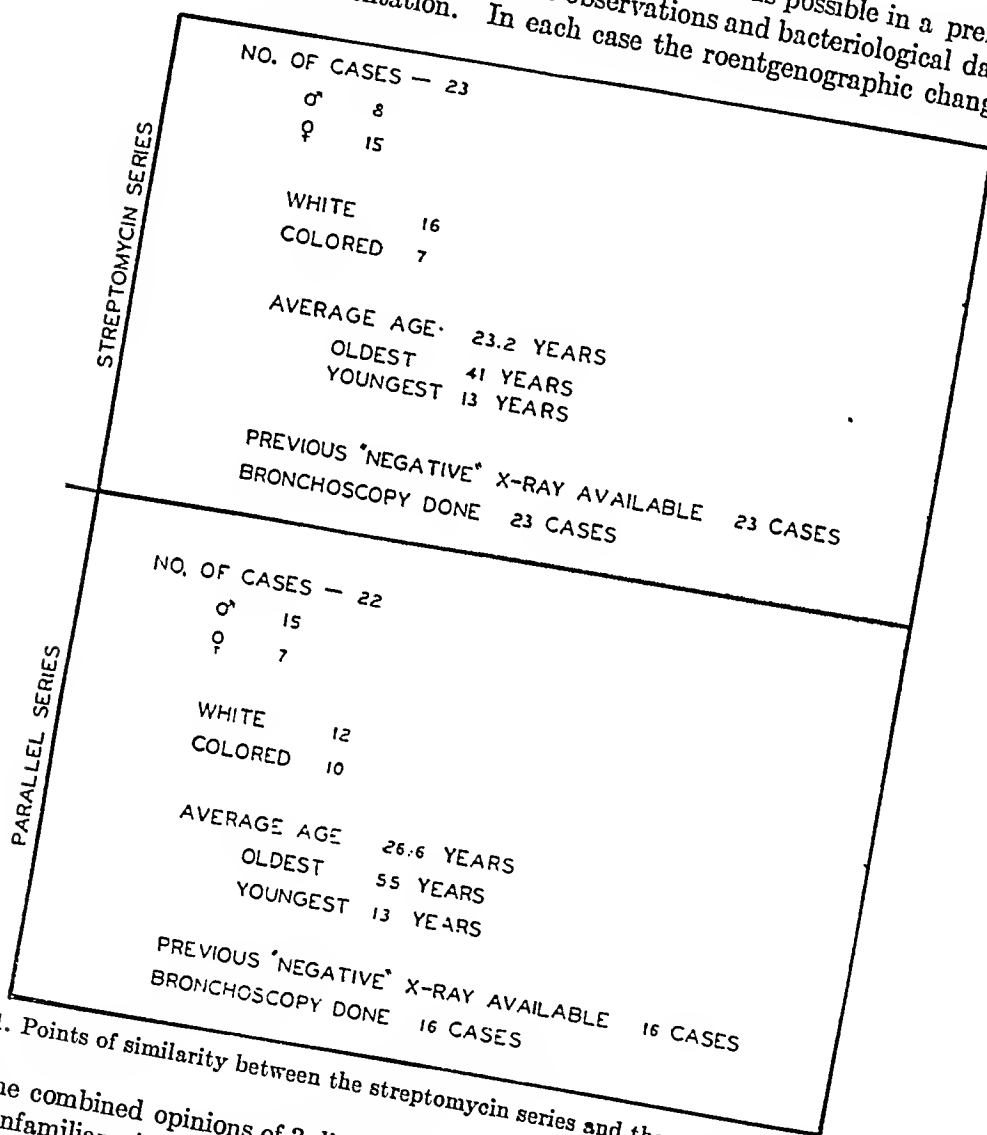


FIG. 1. Points of similarity between the streptomycin series and the parallel series

resent the combined opinions of 3 different observers, at least one of whom was always unfamiliar with the therapeutic program of the individual patient whose roentgenograms were being examined and evaluated.

Figure 2 portrays graphically for each case the onset of roentgenographic regression in days subsequent to the beginning of treatment. To the left of the vertical line the cases are listed in the order of duration of the disease in weeks prior to the onset of therapy. Worthy of emphasis is the fact that the duration

of the pulmonary disease can be accurately evaluated by previous "negative" roentgenograms (see figure 1) or the onset of reliable symptoms, or both. The streptomycin group demonstrated the onset of roentgenographic regression in an average of 22.1 days, while an average of 43.9 days was required for the parallel

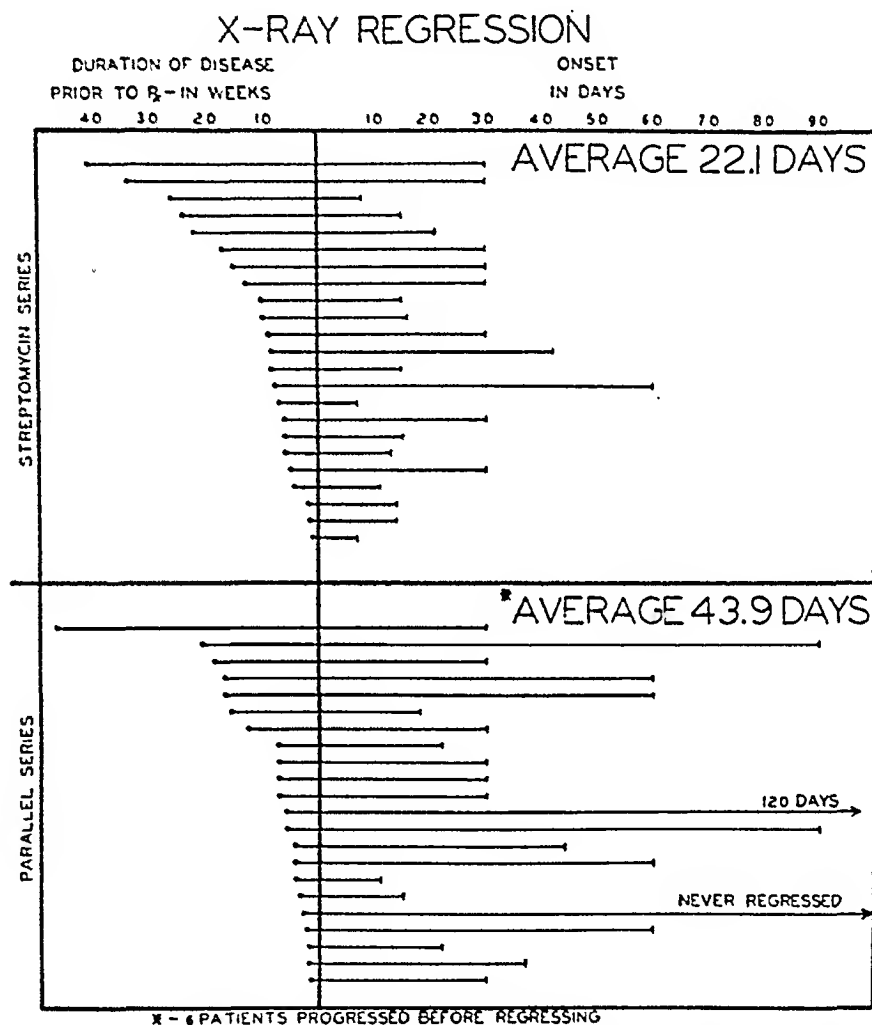


FIG. 2. The vertical line represents the onset of therapy. To the left of this line the cases are listed in the order of duration in weeks of the disease prior to treatment. To the right of the vertical line is the length of time, in days, which elapsed before regression by roentgenogram began to occur.

series. Six of the parallel group actually showed an increase in the extent of their lesions before regression occurred, a phenomenon which never appeared in the streptomycin treated cases. Of interest is the fact that those patients whose disease was of very recent onset showed a rather consistent tendency toward early roentgenographic regression under streptomycin treatment, but no such

consistent tendency could be demonstrated in the patients treated by bed-rest alone.

Figure 3 reveals the amount of regression by roentgenogram, expressed in per cent, which has taken place after one month of therapy. As applied to the right side of the chart, the shorter the line, the greater is the amount of regression and

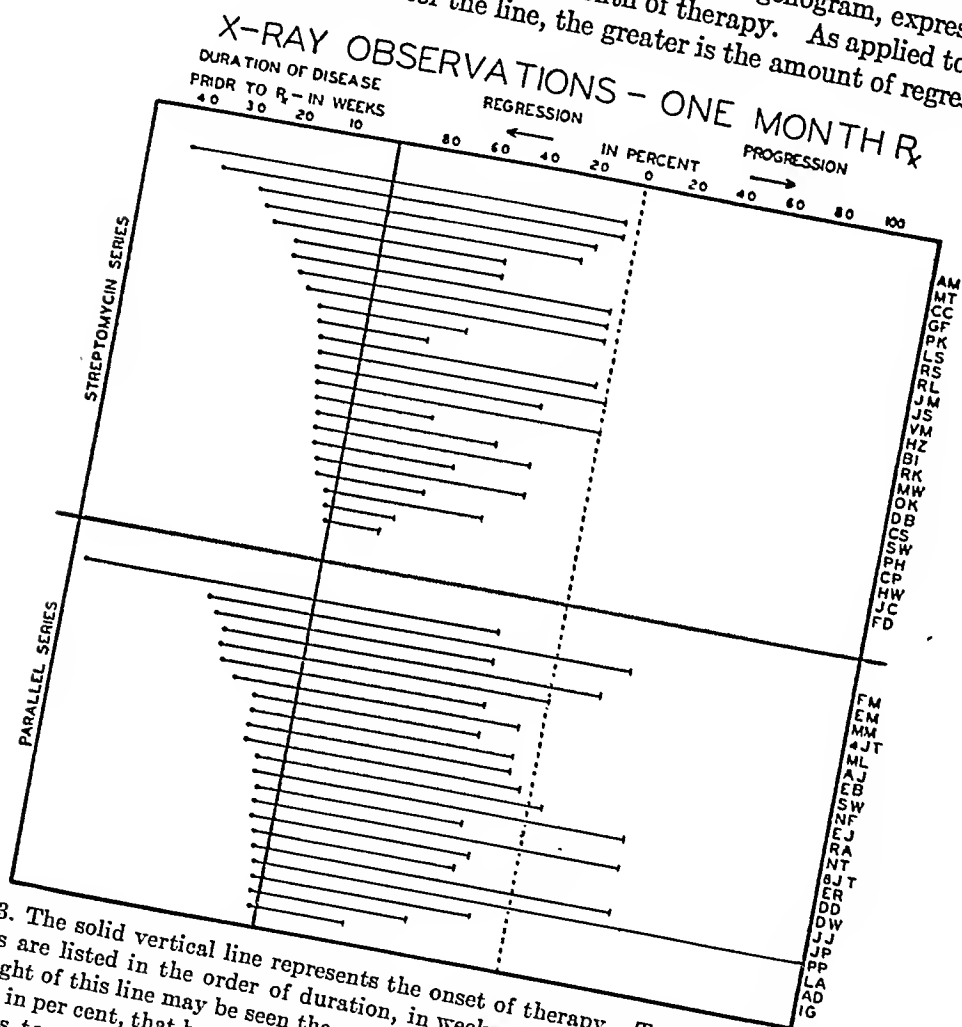


FIG. 3. The solid vertical line represents the onset of therapy. To the left of this line the cases are listed in the order of duration, in weeks, of the disease prior to treatment. To the right of this line may be seen the amount of regression or progression of the lesions, expressed in per cent, that has occurred after one month of treatment. The broken vertical line serves to separate the regressing lesions, which lie to the left of it from the progressing lesions, which extend to the right of it.

any extension of the line to the right beyond "0" indicates actual progression of that lesion. Comparison of the two series demonstrates that, at one month after the start of treatment, no case in the streptomycin series had progressed, while 7 of the parallel group revealed an increase of disease. Noteworthy also is the rather consistently high percentage of clearing in those streptomycin treated cases whose disease was of recent onset.

Figure 4 is a similar presentation showing the percentage of regression by roentgenogram after three months of treatment. The greater amount of regression in the streptomycin series is even more striking at three months than it was at one month.

Figure 5 is an evaluation of the total average clearing at one, three and six months periods, again expressed in per cent. The progressively smaller number of cases in the streptomycin group at three and six months is due to the fact that some of the patients have not as yet completed an equivalent period of treatment.

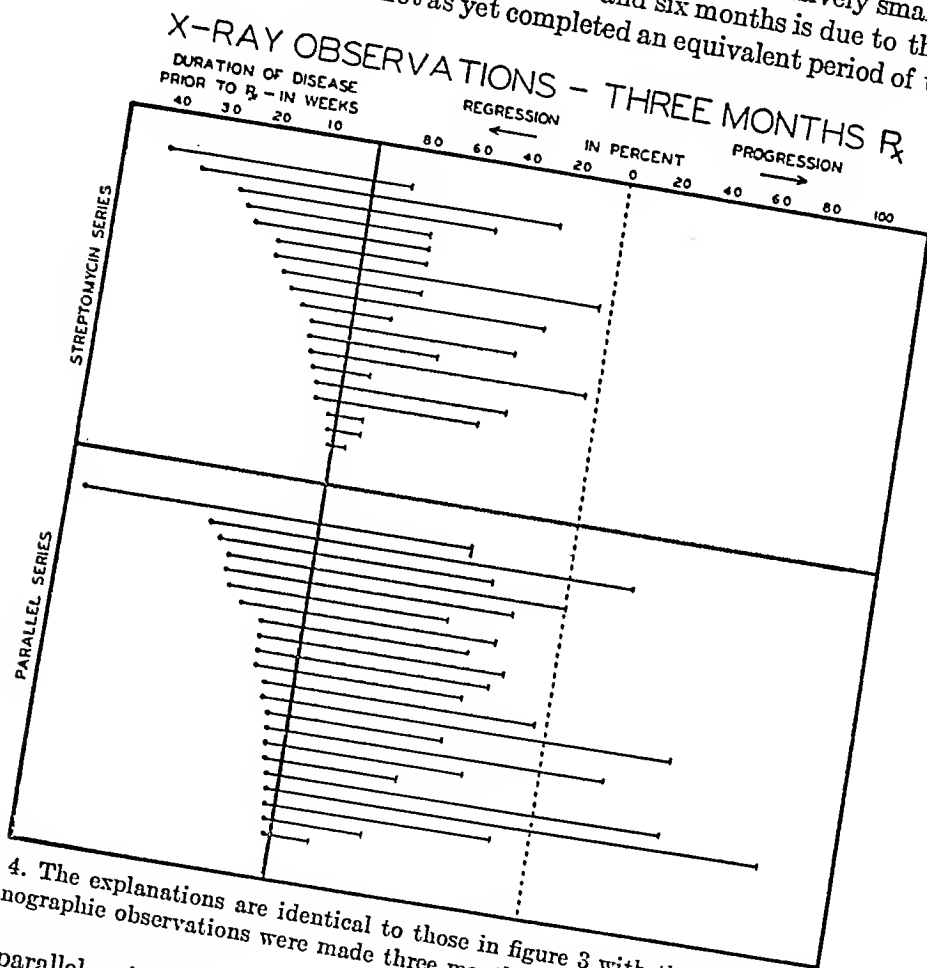


FIG. 4. The explanations are identical to those in figure 3 with the exception that the roentgenographic observations were made three months after the onset of treatment.

In the parallel series the 5 cases omitted at six months were withdrawn because insufficient improvement or progression of their disease made therapy other than bed-rest imperative. If there were a way of computing this into the six-month average, this average would, of course, not appear as favorable as it does.

Figure 6 is similar to the previous chart with the exception that all of the material has been segregated into two groups, designated as "confluent" and "non-confluent." These terms apply to the appearance of the lesion on the roentgenogram: a confluent lesion is characterized by a homogeneous pneumonic type of

infiltration and a nonconfluent lesion by a pneumonia of lobular distribution or a hematogenous type of disease. The justification for such a classification rests in the fact that it appeared to be an objective method of describing the roentgenographic appearance of the lesion. As almost all of the disease in this particular study is of recent onset and thought to be predominantly exudative, both by its

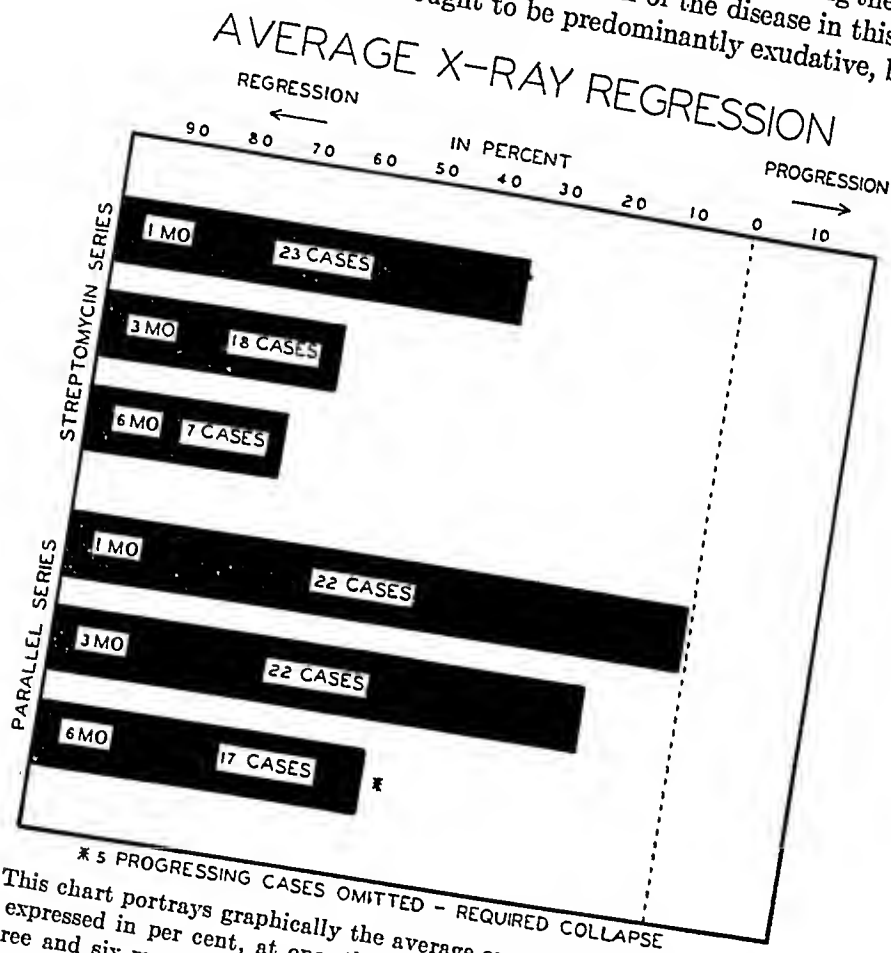


FIG. 5. This chart portrays graphically the average amount of regression on the roentgenogram, expressed in per cent, at one, three and six months. The smaller number of cases at three and six months in the streptomycin series reveals the fact that only this number has completed an equivalent length of treatment. In the parallel series, the 5 cases omitted from the six months' average were necessarily dropped because progression of the disease made necessary the interruption of bed-rest as the sole form of treatment.

roentgenographic appearance and its age, it occurred to us that the usual classifications of exudative and productive could be applied to this project only with the greatest of difficulty. Figure 6 reveals the fact that in the streptomycin series the nonconfluent type of lesion was seen to regress at a much greater rate than did the confluent lesion. At the end of six months of observation the nonconfluent lesions had collectively demonstrated 90 per cent regression. In the parallel series no significant difference in the rate or degree of regression between

confluent and nonconfluent lesions could be demonstrated at one, three or six months.

Figure 7 shows that, of the 18 patients who were positive on concentrate of the sputum or gastric contents at the start of streptomycin therapy, 17 have converted in an average of 38.4 days. Only one patient remains positive on con-

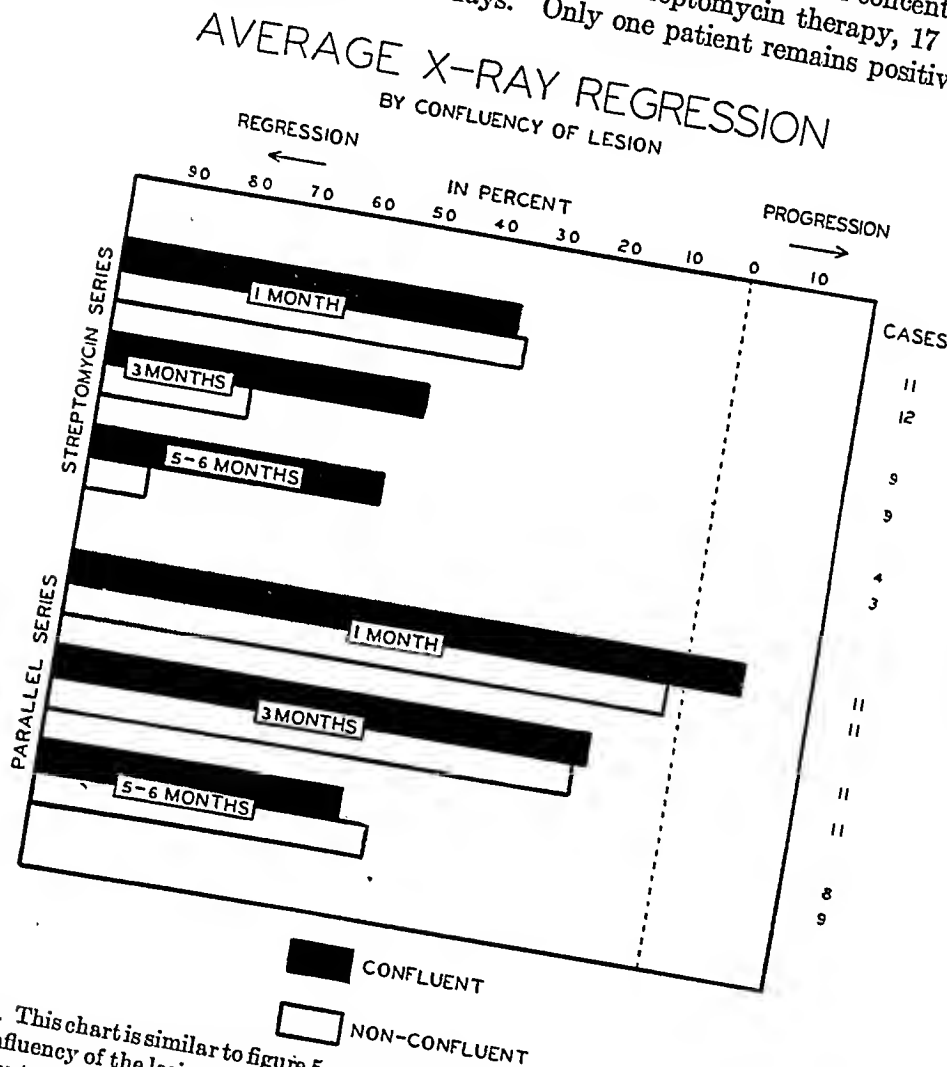


FIG. 6. This chart is similar to figure 5, except that the material has been divided according to the confluency of the lesions. The greater degree of regression of the nonconfluent lesions in the streptomycin series is obvious.

centrate but the duration of treatment in this case has been only twenty-three days. In the parallel series, 9 out of 16 who were positive on concentrate at the start of treatment have converted to negative in an average of 50.7 days. The 7 who are still positive have all had six or more months of treatment. Because much of this study is still in progress the unavoidable delay in the reporting of

the cultures has made it impossible to give a complete culture report at this time. There is to date, however, only one patient who has completed ninety days of streptomycin and who is still positive. The cultures in this case have demonstrated the development of some degree of resistance to streptomycin, the minimum amount of streptomycin required to suppress growth having jumped from

DATA ON BACTERIOLOGY

· SPUTUM AND/OR GASTRIC CONTENTS

		NO. OF CASES - 23	
STREPTOMYCIN SERIES	<u>CONCENTRATE DATA</u>		
	NEGATIVE AT START OF R_x		
	POSITIVE AT START OF R_x	5	
	CONVERTED POSITIVE → NEGATIVE (AVERAGE TIME - 38.4 DAYS)	18	17
	STILL POSITIVE (DURATION OF R_x - 23 DAYS)		1
		NO. OF CASES - 22	
PARALLEL SERIES	<u>CONCENTRATE DATA</u>		
	NEGATIVE AT START OF R_x		
	POSITIVE AT START OF R_x	6	
	CONVERTED POSITIVE → NEGATIVE (AVERAGE TIME - 50.7 DAYS)	16	9
	STILL POSITIVE (DURATION OF R_x - 6+ MONTHS)		7

Fig. 7. Bacillary findings in sputum and gastric content

one microgram per cc. initially to 3 micrograms per cc. within eight weeks after the start of treatment. In the parallel series, 8 are still positive and all 8 have had five or more months of bed-rest.

SUMMARY

1. Two series of patients with roughly comparable disease have been treated, one group with streptomycin and bed-rest, and the other group with bed-rest alone. On the basis of the evidence presented, it appears that streptomycin exerts a beneficial effect upon the course of early pulmonary tuberculosis in excess of what may be obtained by bed-rest as the sole form of treatment. These observations do not extend beyond a period of six months after the initiation of therapy.

2. The earlier in the course of the disease streptomycin therapy is started, the better and more consistent are the results.

3. Streptomycin, in our experience, has exerted a somewhat more beneficial effect thus far upon hematogenous or nonconfluent types of pulmonary infiltrations than upon dense, confluent lesions.

SUMARIO

Efecto de la Estreptomicina sobre las Lesiones Tempranas de la Tuberculosis Pulmonar

1. Dos series de enfermos en estado más o menos comparable fueron tratadas: una con estreptomicina y reposo en cama y la otra solamente con el reposo en cama. Tomando por base los datos presentados, parece que la estreptomicina ejerce un efecto beneficioso sobre la evolución de la tuberculosis pulmonar incipiente, superior al que puede obtenerse con el descanso en cama como único tratamiento. Estas observaciones no abarcaron más de seis meses desde la iniciación del tratamiento.

2. Mientras más temprano en la enfermedad se inicia la estreptomicinoterapia mejor y más constante es el resultado.

3. Según observaron los AA., la estreptomicina ejerció un efecto algo más beneficioso en las formas hematógenas o no confluentes de las infiltraciones pulmonares que en las confluentes y espesas.

The authors are indebted to Dr. John D. Adcock for his many helpful suggestions and advice, to Dr. Cora R. Owen for her technical assistance in preparing the illustrations, and to Dr. Salvatore Yannitelli for his services in behalf of the project.

EFFECT OF STREPTOMYCIN ON EXUDATIVE PULMONARY TUBERCULOSIS^{1, 2, 3}

MYRON W. FISHER,⁴ RALPH L. TINGEY⁵ AND JOHN B. WALLACE⁶

In the spring of 1946, the Army, Navy, and Veterans Administration were allotted streptomycin in sufficient quantity to carry out an investigation of its efficacy in the treatment of tuberculosis. Studies of this nature had been done previously by others, but study of a large number of cases was definitely indicated. This was made possible by the courtesy of the National Research Council.

In Fitzsimons General Hospital, patients with progressive pulmonary exudative tuberculosis with positive bacteriological findings were treated with streptomycin. Dosage was uniform at 2 g. a day given intramuscularly, divided in equal amounts, and the duration of treatment, with few exceptions, was four months. The following tabulations show in an outline manner our results to date:

1. Results of Treatment with Streptomycin

	Cases	Percentage
No improvement.....	12	12
Mediocre.....	37	37
Excellent.....	51	51
Total.....	100	100

2. Pulmonary Tuberculosis Treated with Streptomycin Alone

	Cases	Percentage
No improvement.....	8	14
Mediocre.....	22	39
Excellent.....	27	47
Total.....	57	100

3. Pulmonary Tuberculosis Treated with Streptomycin and Collapse (Pneumothorax and/or Pneumoperitoneum)

	Cases	Percentage
No improvement.....	4	9
Mediocre.....	15	35
Excellent.....	24	56
Total.....	43	100

¹ Presented before the Medical Section, as part of a symposium on *Antibiotics and Chemotherapy in Tuberculosis*, at the 43rd annual meeting of the National Tuberculosis Association, San Francisco, California, June 18, 1947.

² From Fitzsimons General Hospital, Denver, Colorado.

³ This is an abstract of a preliminary report. The complete report with a larger number of treated patients will be published in an early issue of the Review.

⁴ First Lieutenant, SnC.

⁵ Captain, MC.

⁶ Lieutenant Colonel, MC.

STREPTOMYCIN IN PULMONARY TUBERCULOSIS

The use of streptomycin in conjunction with thoracoplasty has been most encouraging; this, in spite of the fact that surgeons are accepting risks now somewhat greater than previously.

In the majority of cases there is a rather definite improvement in the clinical picture. This improvement is usually noted promptly, with a large part of it occurring within the first two months.

4. Results Three to Seven Months after Treatment			
	Disease has progressed	Lesion stationary	Further improvement
Total cases followed 28	7	16	5

Of this relatively small number of cases, 25 per cent progressed when treatment was discontinued. This may be explained in part by the fact that, when many of the patients complete their four months of treatment, they feel so well that it is difficult to persuade them to continue their bed-rest.

SUMMARY

Streptomycin has altered the usual course of the disease in a number of patients with progressive exudative pulmonary tuberculosis. Due to possible, as yet unknown, long-term effects of streptomycin, it has been the policy at Fitzsimons General Hospital not to use streptomycin in patients with minimal involvement who appear to be able to handle the disease adequately without the drug.

SUMARIO

La Estreptomicina en la Tuberculosis Pulmonar Exudativa

Esta reseña expone algunos de los resultados obtenidos en 100 casos de tuberculosis pulmonar tratados con estreptomicina. En varios casos la droga alteró la evolución habitual de la dolencia. Debido a los posibles, aunque desconocidos todavía, efectos tardíos de la estreptomicina, en el Hospital General Fitzsimons tienen por norma no usar la droga en los casos mínimos en los que se cree que el paciente puede atender a la enfermedad adecuadamente sin esta medicación.

EFFECT OF STREPTOMYCIN UPON RECENT TUBERCULOUS PULMONARY INFILTRATION^{1, 2}

R. O. CANADA³

Streptomycin has been shown to exert a suppressive effect upon the course of progressive pulmonary tuberculosis. Some degree of roentgenographic improvement has been observed in acute exudative lesions. Little effect from streptomycin has been observed on far advanced lesions of long standing, on thick-walled cavities or on fibrocaceous disease. From this, it might be expected that roentgenographic improvement would be more readily demonstrated in recent pulmonary infiltration where the destructive processes of tuberculosis have not fully developed.

From a group of 37 cases of progressive pulmonary tuberculosis treated with streptomycin at the U. S. Naval Hospital, Sampson, New York, there were 13 cases with far advanced disease in which new areas of pulmonary infiltration had appeared during the period of hospitalization prior to the use of antibiotic therapy. In order that the roentgenographic changes might be better evaluated, only those cases were included in which shadows consistent with exudative infiltration appeared in previously uninvolved portions of the lung, not immediately adjacent to preëxisting disease. The new lesions had first appeared in chest roentgenograms taken one week to nine months prior to beginning streptomycin therapy, the average known duration being 2.4 months. In 7 cases the new infiltrations had been observed with serial roentgenograms and had either increased in size or, at best, remained stationary. In all cases there was roentgenographic evidence of increasing pulmonary infiltration in other portions of the lung fields and accompanying clinical evidence which indicated a poor prognosis. The sputa were positive for tubercle bacilli on smear and confirmed by culture. Collapse therapy was contraindicated by reason of extent and acuteness of the disease process.

Streptomycin was administered in total daily dosage of 1.8 to 2.4 g. for a period of 120 days. Serial roentgenograms revealed no further increase in size or density of the new infiltration, but did reveal some degree of resolution in all except one case. A significant degree of resolution was observed by the end of one month of treatment in 6 cases, by the end of the second month in 4, and during the third and fourth months of therapy in 2.

Upon completion of the 120 days of therapy, the degree of resolution observed in the new areas of infiltration was considered to be almost complete in one case, marked in 10, moderate in one, and no change in one. The one patient in whom almost complete resolution occurred was a 23-year-old Negro. Pulmonary infiltration first appeared nine months prior to antibiotic therapy while the

¹ Presented before the Medical Section, as part of a symposium on *Antibiotics and Chemotherapy in Tuberculosis*, at the 43rd annual meeting of the National Tuberculosis Association, San Francisco, California, June 18, 1947.

² From the U. S. Naval Hospital, Sampson, New York.

³ Commander, MC, U.S.N.

patient was under treatment for tuberculous lymphadenitis. The infiltration steadily progressed and, at the time streptomycin was instituted, approximately 40 per cent of one lung and 15 per cent of the other were involved with a scattered, predominantly exudative, infiltration. No cavitation was evident. Beginning resolution was observed after two weeks of treatment. Except for a very small area of productive disease in one lung, no parenchymal infiltration was evident in chest roentgenograms taken at completion of treatment. There was concurrent disappearance of draining sinuses, lymphadenitis, as well as complete healing of extensive tuberculous ulceration of the skin.

Of the 10 cases in which resolution was considered to be marked, and one moderate, the new disease was nodular, exudative and diffusely spread throughout an entire lobe or lung in 6, and patchy, exudative, confined to a single lobe in 5. The most marked and complete resolution occurred in those lesions which were nodular and diffusely spread. Little change was observed in those areas of the lung involved with fibrocascous disease.

The one case in which no change was observed in the new pulmonary infiltration had, in addition, advanced fibrocavernous disease and presented a very toxemic clinical course which was not influenced by streptomycin.

With the exception of the last mentioned patient, all experienced a feeling of well-being, decrease of fever, cough and expectoration, and increase of weight, early in the course of treatment. Sputum conversions, according to repeated smears and cultures, occurred in 2 cases. These were the only 2 cases in which cavitation was not present before treatment.

CONCLUSIONS

Spontaneous resolution of pulmonary infiltration which is exudative in nature occurs not infrequently. For this reason, it is difficult to evaluate the rôle of streptomycin in this type of lesion. However, when the prior clinical course is considered, the results appear significant. The 13 patients had far advanced pulmonary tuberculosis and had been treated by complete bed-rest for at least three months prior to streptomycin therapy. Each had shown signs of progressive tuberculosis with loss of weight, fever and roentgenographic evidence of increasing pulmonary infiltration. It appeared unlikely that spontaneous improvement would occur. After four months of antibiotic therapy, it was considered that resolution of marked degree had occurred in the areas of recent pulmonary infiltration in 11 of the 13 cases. Comparison of improvement shown in all exudative lesions revealed more rapid and complete resolution in those lesions of known short duration. The results observed in these 13 cases may be applied in support of the concept advanced by other workers that streptomycin promises real effectiveness in the treatment of pulmonary tuberculosis in which exudative disease of recent origin exists.

CONCLUSIONES

La Estreptomicina en la Infiltración Pulmonar Tuberculosa Reciente

La resolución espontánea de la infiltración pulmonar exudativa no tiene nada de raro, por lo cual resulta difícil justipreciar el papel de la estreptomicina en

las lesiones de dicho género. Sin embargo, después de considerar la evolución clínica anterior, el resultado parece significativo. Los 13 enfermos estudiados tenían tuberculosis pulmonar muy avanzada y habían sido tratados con el descanso en cama absoluto por lo menos desde tres meses antes de la estreptomycinoterapia. Todos habían revelado signos de tuberculosis evolutiva con pérdida de peso, fiebre y hallazgos radiográficos de infiltración pulmonar creciente, pareciendo improbable que se presentara mejoría espontánea. Tras cuatro meses de tratamiento con el antibiótico mencionado, se consideró que había habido resolución pronunciada en las zonas de infiltración pulmonar reciente en 11 de los 13 casos. Una comparación de la mejoría mostrada por todas las lesiones exudativas reveló resolución más rápida y completa en las de duración breve conocida. El resultado observado en estos 13 casos puede tomarse como apoyo del concepto expuesto por otros fisiólogos al efecto de que la estreptomicina promete efectividad real en el tratamiento de la tuberculosis pulmonar cuando existe enfermedad exudativa de origen reciente.

STREPTOMYCIN IN TUBERCULOUS PNEUMONIA^{1, 2}

STANTON T. ALLISON

Pneumonic tuberculosis is believed to be the result of the implantation of the tubercle bacillus upon a highly fertile field. By that I mean an implantation in highly susceptible individuals with little or no resistance to the bacillus. The onset is the same as any reinfection tuberculosis but the symptoms of toxemia are much greater and come on more abruptly. There is first the exudative phase, which, instead of being checked by nature's method of defense, the formation of productive or granulomatous components in the area of involvement, goes on spreading rapidly until an entire lobe or lung may be involved. This is the result so often seen in the Negro, the Porto Rican, and the Indian. It indicates a lack of natural resistance to the infection. Occasionally the patient develops enough resistance early after the infection starts so that this exudative process becomes partly absorbed and partly replaced by productive elements and the pneumonic process comes to a standstill and assumes the characteristics of the usual chronic tuberculous process. More frequently the pneumonic process spreads; cavities develop and the patient dies.

Artificial pneumothorax has been used by most of us with life-saving results in a few of these cases but the fatality rate is high. Pneumonic tuberculous processes are usually ushered in with symptoms of toxemia. There may or may not be chills. The temperature ranges between 101° and 103°F. as a rule but may be higher. The leucocyte count may be within normal limits but may be elevated to 15,000 to 20,000. Usually the total count is lower and the polymorphonuclear percentage considerably lower than in pneumococcal pneumonia. Temperature, pulse and respiration are, as a rule, lower in tuberculous pneumonia than in pneumococcal pneumonia. The respiratory rate in particular is considerably less.

With the advent of streptomycin and as our experience with this drug in treating tuberculosis has increased, it has developed that soft (exudative) processes respond the best; productive processes respond only slightly and predominantly fibrocavernous and fibrotic disease does not respond at all. The question, therefore, has arisen whether this new drug might not take the sting out of this dangerous type of tuberculosis, tuberculous pneumonia. I have found it exceedingly difficult to obtain this type of case for study with the drug. There are many cases of acute exudative spread available every where; but the typical lobar pneumonic tuberculosis, with severe symptoms, such as I have described, is difficult to find, or at least I find it so in New England. I believe it is more common in the South where the Negro population of tuberculous sanatoria is greater. Fortunately I have been able to study an excellent case at the Cushing

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² From the U. S. Veterans Hospital, Rutland, Massachusetts.

STANTON T. ALLISON

General Hospital at Framingham, Massachusetts. Doctor D'Esopo of Sunmount has allowed me to use a case of his for this presentation, I have seen 2 cases at the Chelsea Naval Hospital treated with streptomycin and have had 2 cases of my own. In addition, I have treated 2 patients with far advanced tuberculosis with terminal bronchopneumonic spreads, who were so toxemic that they were placed in oxygen tents and had a life expectancy without the drug of about forty-eight hours. On 3 g. daily these 2 middle-aged patients lost their toxemia rapidly and after four months one is still alive and the other died of a pulmonary embolism from a phlebothrombosis of the leg which came on suddenly. He had improved and been on the drug three weeks when this happened. Although the disappearance of toxemia was striking there was nothing dramatic about the X-ray changes. After a month of treatment no appreciable change could be seen.

From the study of the small group of tuberculous pneumonias certain pertinent observations have been made:

There is lessening of toxemia in all the cases within three to five days following the administration of streptomycin in therapeutic dosage. In 2 of the cases studied this has been true and about equal whether the intramuscular dosage was 6 g. daily or one g. The patient feels better. His appetite increases, his cough diminishes, and chest pain, if there is any, disappears. The temperature drops by lysis within three to seven days to lower levels but usually does not keep to a normal level. It is not the drop commonly seen in lobar pneumococcic pneumonia after sulfa drugs or penicillin. Respiratory and pulse rates become lower. The X-ray changes are not in any sense comparable to the symptomatic improvement and, in these cases, are negligible during the first month of treatment. Apparently once there is true consolidation, it takes time and then more time for the process to resolve and to be replaced by fibrosis.

CONCLUSIONS

Streptomycin probably has a place in the treatment of tuberculous pneumonia. I believe a dosage of 2g. daily for two months, and possibly then an increase to 3 g. daily for a third month is adequate. As we know, the tubercle bacillus is very sensitive to the drug at first but rapidly builds up resistance. After three months of treatment it is questionable whether, due to resistance of the bacilli, any tolerated dosage would have much value.

CONCLUSIONES

La Estreptomicina en la Neumonía Tuberculosa

La estreptomicina tiene probablemente su puesto en el tratamiento de la neumonía tuberculosa. Una dosis de 2 gm. diarios durante dos meses, y luego posiblemente un aumento a 3 gm. diarios por otro mes, parece adecuada. En lo que sepamos, el bacilo tuberculoso se muestra muy sensible a la droga al principio, pero adquiere rápidamente resistencia a la misma. Tras tres meses de tratamiento, es dudoso que, debido a la resistencia de los bacilos, ninguna dosis tolerada posea mucho valor.

EXCRETION OF STREPTOMYCIN INTO TUBERCULOUS CAVITIES, THE PLEURAL SPACE AND THE TRACHEOBRONCHIAL TREE¹

WILLIAM STEENKEN, JR.,² NICHOLAS D. D'ESOP³ AND EMANUEL WOLINSKY²

This study was undertaken to determine in what concentrations streptomycin might be excreted in several body exudates after the drug had been administered intramuscularly. When streptomycin is administered in doses of 1 to 2 g. daily its concentration in the circulating blood is many times the amount necessary to inhibit the growth of the tubercle bacillus. However, the concentrations in those sites at which treatment is directed have not been investigated. It is important to know such local concentrations not only because effective bacteriostatic amounts are therapeutically desirable, but also because minimal concentrations might have the additional disadvantage of enhancing the development of resistant strains. Furthermore, the pleural space and the tracheobronchial tree are accessible to local therapy, and it was thought that data concerning the amount of streptomycin reaching these sites when the drug was given intramuscularly might aid in arriving at a rational approach to such therapy.

This report includes 60 streptomycin assays upon the material recovered from large tuberculous cavities, the tracheobronchial tree, and the pleural space. Specimens were obtained from 13 patients who received streptomycin intramuscularly in doses corresponding to 1.8 to 2.0 g. daily. The individual dose was usually 0.3 g. every four hours. Pus was aspirated from large tuberculous cavities by the Monaldi technique of cavity drainage. It was necessary to drain most cavities four to six hours before material sufficient for assay was obtained. Blood for streptomycin assay was taken in most instances at the beginning of cavity drainage, which was usually one hour after the drug had been administered. Material was aspirated from the tracheobronchial tree during bronchoscopy, care having been taken to avoid pharyngeal and laryngeal secretions. Blood for streptomycin assay was withdrawn from an arm vein a few moments before bronchoscopy. Specimens were obtained from the pleural spaces of patients who had serous or purulent tuberculous effusions. Streptomycin in all specimens was assayed by the cup-plate method of Stebbins using *Staphylococcus aureus*, SM strain.

Twenty-four specimens of material aspirated from large tuberculous cavities were assayed. The average concentration of streptomycin in these was 7.7 micrograms per cc. The lowest concentration was one microgram, the highest 18.0 micrograms per cc. The average concentration of the drug in the blood obtained at the beginning of cavity drainage was 13.3 micrograms per cc.

Six specimens from the pleural space were assayed. The average amount in

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² Research and Clinical Laboratory, Trudeau Sanatorium, Trudeau, New York.

³ Veterans Administration Hospital, Sunmount, New York.

STEENKEN, D'ESOPO AND WOLINSKY

these was 8.8 micrograms per cc.; the lowest being one microgram, and the highest 14.0 micrograms per cc. The average concentration of streptomycin in the blood drawn at the time of thoracocentesis was 12.2 micrograms per cc.

There were 4 specimens of material aspirated from the tracheobronchial tree. The average concentration of streptomycin was 12.1 micrograms per cc.; the lowest value was 6.5 micrograms, and the highest was 20 micrograms per cc. The average blood streptomycin was 11.0 micrograms per cc.

CONCLUSIONS

When streptomycin is administered every four hours in a total daily dose of 1.8 to 2.0 g., the average concentrations in large tuberculous cavities, the pleural space, and the tracheobronchial tree are much greater than those which completely inhibit the growth of tubercle bacilli *in vitro*.

CONCLUSIONES

*Excreción de Estreptomicina a las Cavernas Tuberculosas,
el Espacio Pleural y al Arbol Traqueobronquial*

Ad administrar estreptomicina cada cuatro horas hasta una dosis diaria total de 1.8 a 2.0 gm., las concentraciones medias obtenidas en las grandes cavernas tuberculosas, el espacio pleural y el árbol traqueobronquial son mucho mayores que las que inhiben completamente el desarrollo de los bacilos tuberculosos *in vitro*.

STREPTOMYCIN IN TUBERCULOUS LARYNGITIS^{1,2}

MYLES BLACK AND EMIL BOGEN

Since January, 1947, at the Olive View Sanatorium, 34 patients with the extra-pulmonary complication of tuberculous laryngitis have been treated with streptomycin, (1) either systemically or locally, using a spray of 10 per cent streptomycin solution. Of these 34 patients, 28 had been previously followed over a period of several months under some other form of therapy, such as promin, ultraviolet light or electrocautery, without showing any definite improvement objectively or symptomically.

Originally, 15 cases were treated locally with streptomycin spray applied to the larynx in six equal doses evenly spaced through the waking hours. Four of the patients in whom there was no improvement in the first month of treatment later successfully received the drug by the intramuscular route. In one other who had become worse under aerosol treatment, the first intramuscular injection produced a severe state of shock or histamine-like reaction within a few seconds. No further injections were given this patient. Three other patients showed definite progression of the disease, one of whom has since died. In 2 more cases, in both of whom there was previously visible ulceration, there is now no sign of active disease on the larynx.

In 3 cases a mixture of one gram of streptomycin, one gram of promin in a 2 per cent solution of trypan blue was used (2). However, this mixture seemed to produce no more favorable results than the streptomycin aerosol. One fact was noted that might be advantageous, and that is that ulcers were stained a bright blue and the normal or edematous mucosa retained the original color.

All 3 cases given only 0.5 g. showed improvement within six weeks. In one case there was initially severe dysphagia and occasionally episodes of severe coughing that started by laryngeal irritation. At the present time there is still evidence of active disease in the larynx, but the patient can now speak with an audible voice and the pain and dysphagia have subsided. In the second case there was marked improvement in less than two weeks after treatment was started, in the other after one month.

Eleven cases received one gram daily. In one, the total dose was given in five equal doses; in 3, three doses; and in the other 7, only two injections of 0.5 g. each were given. In 4 of the cases there is now no evidence of active disease. In the other 7 cases there is definite improvement. In 5 cases there was pain and dysphagia. These symptoms disappeared in less than a week after therapy was instituted. Several patients who had experienced continuous tickling in the throat also experienced relief from this symptom.

Nine cases received 2 g. daily in five equal doses. Seven of these now show no

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² From the Olive View Sanatorium, Olive View, California.

evidence of active disease and the other 2 have shown definite improvement. In one of the cases that still has activity, the initial lesion was severe epiglottic ulceration. Treatment by electrocautery in the latter part of 1946 helped the condition somewhat. At the onset of the streptomycin therapy several small caseous nodules were noted on the posterior surface of the epiglottis. Although the voice is stronger and there is less subjective irritation, there has been little change in the appearance of the larynx. On these cases there has been a period of four to nine weeks' observation after therapy was stopped. Of the 7 that cleared completely, in none is there evidence of new or reactivated disease. In one case that showed improvement initially, there has been noted recently (eight weeks after treatment stopped) evidence of voice fatigue and laryngeal irritation. However, there has been no visible change in the larynx.

In the same period of treatment a 2 g. daily dose was more effective than small doses of the drug. However, the effect did not reach the desired level until after the appearance of signs of vestibular disturbance. In this small series there was definite improvement in cases receiving as low as 0.5 g. The small dose has the advantage of not producing any marked disturbance in vestibular function. Even in one gram dose the amount of vestibular disturbance is much less than on the 2 g. dose. In patients receiving 2 g. there has been discomfort from the continued disturbance in vestibular function. Accordingly it may seem more advantageous to use the smaller dose even though the progress is not so rapid. One factor that might deter the use of small doses in the face of improvement would be the development of streptomycin resistant organisms (3).

In all the cases the pulmonary condition was moderately or far advanced. The laryngeal lesion was moderately severe or severe with evidence of ulceration or granulation tissue. The laryngeal lesions improved although the pulmonary lesions remained stationary or progressed during the same interval in many cases.

*Results of streptomycin treatment in laryngeal tuberculosis,
compared with other forms of therapy*

	HEALED	IMPROVED	SAME	WORSE	TOTAL
Streptomycin					
2 g. intramuscularly.....	7	2			9
1 g. intramuscularly.....	4	7	0	0	11
0.5 g. intramuscularly.....	0	3	0	0	3
0.5 g. aerosol.....	2	5	4	4	15
Promin aerosol.....	4	6	3	7	20
Penicillin aerosol.....	3	1	1	5	10
Ultraviolet and cautery.....	2	6	4	18	30

In 30 similar cases treated at the Olive View Sanatorium during the past year, only with ultraviolet radiation and cautery, with voice rest and general sanatorium care, only 2 appeared healed and 6 improved, with 22 unimproved or

STREPTOMYCIN IN EXTRAPULMONARY TUBERCULOSIS

worse. In 30 cases treated with promin or penicillin aerosol, 7 healed and 7 improved, with 16 unimproved or worse. In 34 treated with streptomycin in varying doses and routes, 13 healed and 17 improved, with only 4 unimproved or worse. Streptomycin has been, in our experience, by far the most effective treatment so far known for tuberculous laryngitis.

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STREPTOMYCIN IN TUBERCULOUS TRACHEOBRONCHITIS¹

LYMAN A. BREWER, III² AND EMIL BOGEN³

Direct observation of the course of readily accessible visible lesions are especially useful in the evaluation of a new therapeutic agent to combat tuberculous infection in man. Tuberculous ulcerations and granulations of the trachea and larger bronchi which may be seen on bronchoscopic examination are particularly suitable for such an evaluation. These lesions are encountered often enough to make such a study feasible. They are of grave prognostic import. They are either completely refractory to previously tried methods of therapy or are sufficiently sluggish in healing, so that response to treatment can be readily appreciated. This report is based on the study of the therapeutic effect of streptomycin on persistent, severe ulcerations and granulations of the trachea and larger bronchi in 44 patients who were selected from a large number of persons considered for this treatment, showing various types of tuberculous tracheobronchitis. These patients were studied at the Veterans Administration Hospital, San Fernando, California and the Los Angeles County Tuberculosis Sanatorium, Olive View, California.

Tuberculous tracheobronchitis has become recognized during the past decade as a frequent complication of pulmonary tuberculosis, which interferes with respiratory function, leads to spread of the disease, and often precludes the application of collapse measures otherwise indicated. Although many of these cases eventually heal by resolution or by scarring, which in turn may lead to fibrous stenosis with further complications, the usual course is slow and fraught with danger of spreads and interference with bronchial drainage with disastrous effect on the pulmonary lesion.

SELECTION OF CLINICAL MATERIAL

This study was based upon 44 cases selected from over 300, considered as possible candidates for streptomycin therapy for tuberculous tracheobronchitis. The bronchoscopic findings of these patients were reviewed because of suggestive clinical, radiological and bronchoscopic evidence of tracheal or bronchial involvement. These bronchoscopic findings included hyperemia and edema of the bronchial mucosa, "submucosal" lesions, fibrous stenoses and ulcerations and granulations of the tracheal and bronchial mucous membrane. Hyperemia and edema of the mucous membrane, although often considered as evidence of an early tuberculous tracheobronchitis, are frequently seen in other conditions. These lesions come and go and may only reflect the amount of infected sputum passing over any given portion of the bronchus. Opacity and irregularity of

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² 1930 Wilshire Blvd., Los Angeles, California.

³ Olive View Sanatorium, Olive View, California.

the bronchial lining, sometimes interpreted as representing submucosal nodulations, are not fit subjects for such a study because the intact mucosa covering these lesions makes an accurate evaluation of changes difficult. Healed fibrous stenosis could not be expected to change with any antibiotic therapy and so were rejected for this study. Since superficial ulcerations sometimes show a tendency toward spontaneous healing, they were not treated at once but observed over a period of time. Only patients with persistent and progressive ulcers and granulations were considered satisfactory subjects for the evaluation of streptomycin therapy.

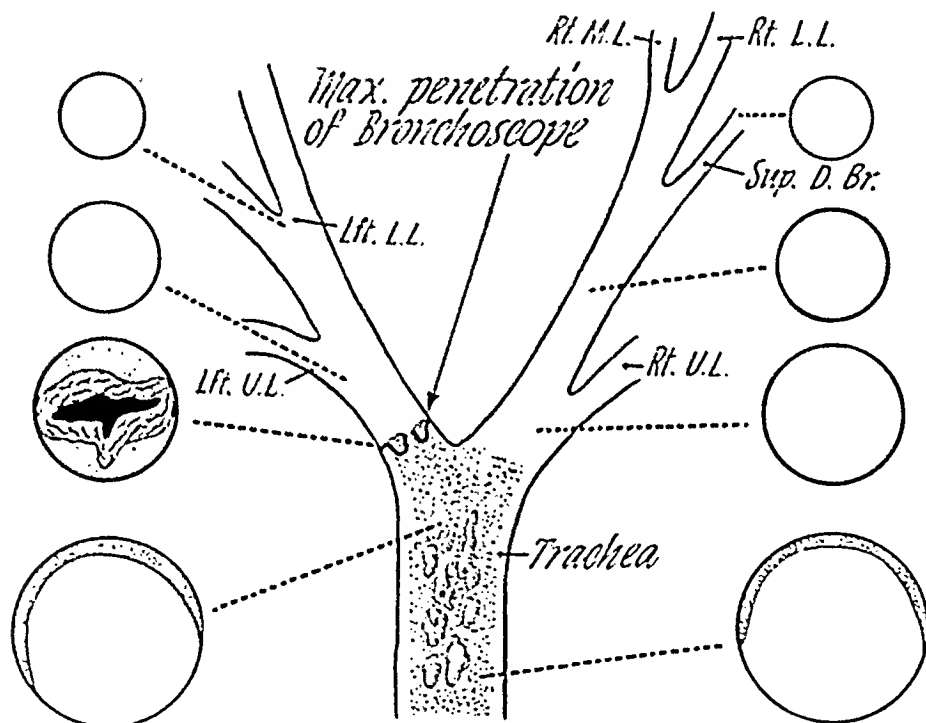


FIG. 1. Graphic record of typical case before treatment. Bronchoscopic examination record.

Bronchoscopic findings before and at fortnightly intervals, after starting the treatment, were recorded graphically and analytically on charts developed especially for this study. (See figure 1 and table 1.)

Patients selected for the treatment were all given careful preliminary clinical, bronchoscopic, radiological and laboratory examinations and told of the experimental nature of the treatment and its possible ill effects. All were on a continuous bed-rest regimen with toilet privileges throughout the course of the treatment. No new forms of collapse therapy were initiated during the treatment period, but those already carrying pneumoperitoneum or pneumothorax were continued in a similar manner throughout this time.

TABLE 1
Analytical tabulation of bronchoscopic findings
(Same case as shown in figure 1)

	EXCRE- TION	HYPER- EMIA	EDEMA	GRANU- LATION	ULCER- ATION	STENOSIS	SCAR
Larynx							
Epiglottis.....	—	—	—	—	—	—	—
Arytenoids.....	—	—	—	—	—	—	—
Posterior space.....	—	—	—	—	—	—	—
Cords.....	—	—	—	—	—	—	—
Trachea							
Upper third.....	—	—	—	—	—	—	—
Middle third.....	—	—	—	—	—	—	—
Lower third.....	xxx	xxx	xxx	—	—	—	—
Carina.....	xxx	xxx	xxx	—	—	—	—
Right	—	xx	—	—	—	—	—
Main bronchus.....	—	—	—	—	—	—	—
Upper lobe orifice.....	—	—	—	—	—	—	—
Bronchus intermedius.....	—	—	—	—	—	—	—
Middle lobe bronchus.....	—	—	—	—	—	—	—
Lower lobe bronchus.....	—	—	—	—	—	—	—
Left							
Main bronchus.....	—	—	—	—	—	—	—
Upper lobe orifice.....	—	xxx	—	—	—	—	—
Lower lobe bronchus.....	—	—	xxx	xxx	66%	—	—
Summary:	1. Extensive ulcer and granulation of left main bronchus producing 66 per cent reduction in lumen of bronchus.	2. Hyperemia and edema, entire trachea.	3. Moderate amount sputum in lower trachea.				

METHOD OF TREATMENT

Treatment was given first to a series of 13 such patients by the combined inhalation and intramuscular route, with large dosage of a total of 2.4 to 3.0 g. daily in order to determine whether such treatment of maximum tolerated amounts might be effective. Both the streptomycin hydrochloride manufactured by Merck and the streptomycin sulfate manufactured by Pfizer, although sometimes distributed through other concerns, were used with little apparent difference except for the greater bulkiness and less complete solubility of the sulfate. Certain lots of both preparations appeared to produce more local irritation.

For intramuscular use, isotonic saline solution was added to the one gram of streptomycin in the original commercial container, making it up at first to 5 cc. One and one-half cc. of this solution, or 0.3 g., were injected intramuscularly deeply in the gluteal region, every four hours. Later the dose was increased to

2.0 cc., so the daily dose varied from 1.8 to 2.4 g. by this route, in addition to the amount given by aerosol. It was intended, originally, to continue the treatment for a full ninety days in all cases, but, because of toxemia in a few cases and later because of interest regarding the permanence of apparent early cures, the treatments were generally discontinued before that time.

Streptomycin has been administered by aerosol as follows: One gram of streptomycin is dissolved in 8 cc. of distilled water. One-half cc. of this solution is placed in the aerosol apparatus for inhalation each two hours, from 6 a.m. to 8 p.m., making 8 treatments or a total of 0.5 g. of streptomycin inhaled daily. The streptomycin is usually administered through a "vaporizer" such as that manufactured by Parke, Davis & Co. for adrenalin, or a De Vilbiss "nebulizer" which is attached by a long rubber tube to a large (Type H) tank of oxygen, equipped with a valve and pressure regulator. The oxygen is turned on to flow at the rate of about 6 liters per minute during the treatments, which last on the average about a quarter of an hour. A small hole is bored (or burned) in the rubber tubing just near its distal attachment so that the patient can cover it with his finger during inhalation, when taking the treatment, but uncover it, allowing the oxygen to escape, during exhalation without wasting the solution. A small amount of sticky material remains in the vaporizer after each treatment and, if this is allowed to accumulate, it plugs the apparatus. Accordingly, a medicine glass full of distilled water and a medicine dropper is left at the bedside and one or more times a day, as seems needed, the patient adds a drop of water (about 1 cc.) to the drying sediment, and inhales this as an extra aerosol treatment after a regular one, thus preventing waste of the active material in the sediment and saving the nurses the task of cleaning out the vaporizer. Some patients need to be warned to inhale the aerosol naturally, and not to take unusually deep breaths which may tire them, in the hope of greater absorption, but they soon become adept at inhaling and turning off the aerosol by removing their finger from the side hole in the rubber tubing during exhalation. Other methods of administering streptomycin aerosol are feasible, but the above has been used for more than one year in this Hospital and has proved satisfactory.

RESULTS OF COMBINED INTRAMUSCULAR AND AEROSOL TREATMENT

Between August and December, 1946, 13 patients, carefully selected from more than 100 referred for this purpose, were started on the combined aerosol and intramuscular treatment. Without exception, repeated bronchoscopic examinations showed regression of the lesion within two weeks after starting the treatment, and in every case all evidence of active ulceration or granulation had cleared up within two months. The subsidence of inflammation and edema, the regeneration of the epithelium covering over the ulcerations and the disappearance of granulations in these patients were striking. In many of them, abundant positive sputum from remaining pulmonary cavities continued to bathe the mucosa, arousing hyperemia and edema. Nevertheless, the mucosal ulcerations and granulations healed despite this continued irritation.

RESULTS WITH AEROSOL TREATMENT

Although it was originally proposed that this treatment be given to 20 patients, the good results consistently obtained in the first 13 cases led us to discontinue this regimen in favor of further experimental studies. We were especially anxious to discover, at first, whether the local administration of streptomycin by aerosol alone, without an intramuscular treatment, would suffice. This would have great advantages, not only in lessening the cost, pain and inconvenience of the injections, but also probably avoiding the toxic effects, especially the ves-tibular paralysis which developed in all the patients given the combined treatment for the full period. Twelve patients received this aerosol treatment alone and all showed some improvement, but in only 4 was the healing apparently complete within a month of starting.

In 4 cases, 0.5 g. of promin and 10 mg. trypan blue were combined with the streptomycin inhalations, but the results with these two adjuvants did not appear strikingly better than with the streptomycin aerosol alone; 2 healed and 2 improved within two months.

RESULTS WITH INTRAMUSCULAR TREATMENT

All of the 13 patients treated with the intramuscular injections of 2 g. of streptomycin daily without aerosol responded by healing. Since it became evident, accordingly, that we could not hope for as rapid or complete healing from the inhalation of streptomycin aerosol alone, as had been observed with the intra-

TABLE 2
Results of streptomycin therapy in tuberculous tracheobronchitis

	COMBINED INTRAMUSCULAR AND AEROSOL	INTRAMUSCULAR ALONE		AEROSOL ALONE
		2 g.	1 g. or less	
Healed.....	13	13	6	4
Improved.....	0	0	4	2
Unimproved.....	0	0	2	6

muscular route alone or the combined route, further attention was paid to the possibility of obtaining results with smaller doses than the 1.8 to 2.4 g. previously given intramuscularly. Eight patients given one gram a day, intramuscularly, chiefly in two doses of 0.5 g. each, all improved though only 5 had completely healed at the end of two months. Four patients were started on as little as 0.5 g., in a single injection, daily and all of these showed marked improvement, but only one showed complete healing when examined one month later. It is recognized that all of these series are small, and not entirely complete or comparable. (See table 2.)

The aerosol groups had smaller daily doses than most of those receiving intramuscular and combined treatments. The aerosol inhalations alone or the smaller intramuscular injections were also not administered for a full three months' period. Although improvement

was noted on the shorter, smaller and local regimens, it was slower and less complete than with the larger intramuscular or combined treatments. All of the cultures tested before starting treatment were highly susceptible to streptomycin, but resistance to high concentrations developed in some but not all of them within a few months. Enough information is not yet available as to whether the development of resistance, or other factors, make the more rapid healing of sufficient importance to warrant the larger doses.

COURSE OF PULMONARY LESIONS

Pulmonary cavities in these patients remained open, and although temporary symptomatic and clinical improvement was noted in other lesions in the lungs, and the sputum was markedly reduced or became temporarily negative in others, this amelioration was not sustained. Nevertheless, in only 3 instances has a recurrence of such ulcerative or granulating tuberculous tracheobronchial lesion been noted since discontinuance of treatment.

Despite the complete healing of ulcerative or granulating lesions, fibrous stenoses present in these patients persisted throughout the treatment, and even resisted repeated dilations and aspirations, with resultant local atelectasis, impaired drainage and toxemia in several patients. Thoracoplasties have been completed on 4 of the patients originally given the combined treatment and have been started, or are projected, on several of the more recent ones who have responded to the intramuscular treatment alone.

TOXEMIC MANIFESTATION

Our first patient with a local ulcer on the wall of the trachea healed following only one week of treatment, which was discontinued because of severe systemic reactions, with a petechial rash, fever and hematuria. Two patients, with impaired renal function, developed anuria and blood levels of 80 micrograms of streptomycin per cc. within a week after starting treatment and treatment, accordingly, was discontinued, but in both cases the tracheobronchial lesions continued to heal and remained so, although one of these patients died six weeks later. Other toxemic phenomena included anorexia, nausea, vomiting, vertigo, tinnitus, stomatitis, eosinophilia, etc.; however none of our patients has shown loss of hearing; in fact, several report improvement. All receiving 2 g. daily for over two months and some of those receiving one gram have lost their vestibular function as shown by symptoms and the caloric test, but most of them learned to compensate fairly well.

STREPTOMYCIN DETERMINATIONS

Repeated biological assay showed only traces of streptomycin in the blood and urine following aerosol alone, and only small amounts could be detected in the sputum following intramuscular injections alone. Blood levels following intramuscular injections generally averaged from 10 to 20 units about two hours after an injection but were higher following the larger doses in patients with low renal function and in smaller patients. Toxemic symptoms were more frequent

in patients with higher blood levels but therapeutic correlation cannot yet be established.

CONCLUSIONS

This study indicates that streptomycin is a valuable therapeutic agent in the treatment of the most severe types of active tuberculous tracheobronchitis, the most effective, in fact, which we have ever seen. Preliminary data regarding dosage and route of administration have been presented but further work is needed on these problems.

SUMMARY

Forty-four patients with persistent severe ulcerating or granulating tuberculous lesions of the trachea and larger bronchi have been treated with streptomycin. Thirteen patients given combined intramuscular and aerosol inhalation treatment and 13 given larger doses of streptomycin intramuscularly, all showed rapid complete healing. Less rapid and less uniform results were obtained in 12 patients who received smaller doses intramuscularly and in 12 patients treated by aerosol alone. Such rapid and complete healing has not been observed in other patients with similar lesions observed previously or simultaneously under different therapeutic regimens.

SUMARIO

La Estreptomicina en la Traqueobronquitis Tuberculosa

A 44 enfermos con persistentes y graves lesiones tuberculosas ulceradas o granuladas de la tráquea y bronquios mayores se les trató con estreptomicina. Trece que recibieron tratamiento combinado por vía intramuscular y en inhalación de aerosoles y 13 que recibieron dosis mayores de estreptomicina intramuscularmente, curaron rápida y completamente. En 12 enfermos que recibieron dosis menores por vía muscular y en 12 tratados exclusivamente con aerosoles, el resultado fué menos rápido y uniforme. En otros enfermos con lesiones semejantes, observados previa o simultáneamente mientras recibían terapéuticas distintas, no se ha notado una curación tan rápida y completa como la anterior.

This study was carried out under the auspices of the Tuberculosis Division of the U. S. Veterans Administration and the Subcommittee on Streptomycin of the American Trudeau Society, with the generous and whole-hearted aid of the staff of the San Fernando Veterans Hospital and the Olive View Sanatorium; but all conclusions and opinions expressed herein are the sole responsibility of the authors, and do not necessarily represent the policy of the above named organizations.

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STREPTOMYCIN IN TUBERCULOUS ENTERITIS^{1,2,3}

HENRY C. SWEANY

Tuberculosis of the gastro-intestinal tract was not noted among the first cases treated by Hinshaw and associates, and since then, the complication has been observed largely as an associated condition in patients treated for pulmonary lesions. There have been a few cases, however, where the symptoms of enteritis were so severe that treatment was directed primarily at the enteritis. The results have been so phenomenal in many of these cases that it seemed justifiable to assemble as many as possible for this symposium. With the permission of the Streptomycin Committee of the Veterans Administration, I am submitting a composite summary of 8 cases from the Veterans Hospitals, together with 3 others from civilian hospitals. The 3 cases reported are as follows: one brief history from the Municipal Tuberculosis Sanitarium of Chicago, and 2 furnished by Dr. B. C. Bellinger of the Oregon State Tuberculosis Hospital.

Diagnosis was generally made by the X-ray film, and clinical symptoms of pain, tenderness, anorexia, nausea and diarrhea.

At the Municipal Tuberculosis Sanitarium, 11 cases of suspected tuberculous enteritis have been treated to date (September 23, 1947), but only 2 have had evidence to warrant an unequivocal diagnosis of enteritis, one as a result of the removal of a tuberculous appendix and another by virtue of a definite X-ray pattern on barium enema. Both had the common clinical symptoms. Practically all of the other 9 cases showed some improvement in the symptoms of enteritis rather early in the course of the treatment. The second of the 2 cases with absolute findings of enteritis will be reported in lieu of those from the Veterans Hospitals which were given in the original report but, because of previous commitment, cannot be given here.

CASE REPORTS

Case 1: The patient, H. McV., was a 34-year-old man of Scotch-Norwegian descent. His pulmonary tuberculosis was discovered in 1944, after which he had a brief stay in the Municipal Tuberculosis Sanitarium (Chicago). On February 13, 1947, he reentered the hospital complaining of colicky pains in the abdomen, with associated fever up to 101.5°F., weight loss, and diarrhea. Owing to the fact that the colon was palpable and tender and to the many subjective signs, Dr. George Turner made a diagnosis of "probable tuberculous enteritis, with F. A. B. pulmonary tuberculosis." The suspicion of enteritis was confirmed by Dr. Warren Furey who found, among other things, on X-ray examination:

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² From the City of Chicago Municipal Tuberculosis Sanitarium, the Hines Veterans Hospital, Hines, Illinois, and Northwestern University Medical School, Chicago, Illinois.

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"a very marked spasm of the ascending colon and cecum. The mucosal pattern in this area is roughened and irregular. Conclusion: Tuberculosis of the colon." Accordingly, the Streptomycin Board recommended treatment for the enteritis. The streptomycin treatment was begun on May 2, 1947, and has been continued to the present time (September 23, 1947). On July 5, 1947, after sixty days of treatment of 2 g. a day in five divided doses, there was marked improvement of the symptoms of enteritis and a clearing of the chest X-ray. On August 6, 1947, there was further clearing of the chest X-ray, the diarrhea had stopped, and the general condition of the patient had greatly improved. At this time the dosage was changed to 1.5 g. in three divided and equally spaced doses. It was thought advisable to give another sixty days of treatment. On September 10, 1947, still further improvement prompted the Board to recommend a total of 180 days of treatment.

Dr. Morris Weissman's last report on the clinical condition of the patient revealed that the pain, diarrhea, and tenderness of the bowels had disappeared; the temperature had become normal; the pulse had decreased from 108 to 88; the weight gain was 33½ pounds (134 to 167½ pounds); the sputum had decreased from 50 to 75 cc. to around 10 cc., but was still positive for tubercle bacilli; the general condition of the patient was good, and he felt well.

This case derives much interest from the fact that improvement was continuous for nearly five months and the patient suffered no ill effects from the drug during that time.

Case 2: F. R., #5320, Oregon State Tuberculosis Hospital, had moderately advanced bilateral pulmonary tuberculosis with a temperature from 99° to 101°F., positive sputum and progressive loss of weight. Tuberculous enteritis was diagnosed by symptoms of anorexia, loss of weight, abdominal pain and tenderness, and by a barium meal. After ten to fourteen days of treatment with 1 g. a day of streptomycin in grape juice, the anorexia, tenderness and abdominal pain disappeared, but the X-ray findings were unchanged after twenty-one days. The blood findings were all improved: the polynuclears changed from 13,700 to 9,600; the neutrophils from 83 to 61 per cent; the sedimentation rate decreased slightly. There were no other significant changes.

Case 3: E. P., #5358, of the Oregon State Tuberculosis Hospital, had far advanced bilateral pulmonary tuberculosis with positive sputum and a miliary spread and pleural effusion. Tubercle bacilli were found in the urine, but renal disease was not proved. There was a marked loss of weight and the patient was in poor condition. Tuberculous enteritis was diagnosed by symptoms of anorexia, slight abdominal discomfort, and by a characteristic pattern following a barium meal. Two grams of streptomycin were given daily, but stopped after fourteen days. After the treatment, there was improvement in the anorexia and discomfort within the week; the white blood count changed from 10,400 to 6,450; the neutrophils from 81.5 to 69.5 per cent; and the lymphocytes from 12.5 to 20 per cent. All other findings were unchanged or worse.

SUMMARY

It is too soon and our material is too limited to draw any definitive conclusions from the results of streptomycin treatment of tuberculous enteritis. There were certain consistent favorable results which are briefly as follows: an improved feeling of well-being; anorexia, pain, discomfort and tenderness in the abdomen almost entirely disappeared within three to ten days after treatment

was begun; diarrhea disappeared usually within two weeks; roentgenological signs (present in most cases) generally showed only slight to moderate improvement there was marked gain in weight in 10 cases and the general condition was improved in these. One case was improved enough for successful lung surgery; a few cases had a decrease of sputum, although none turned negative as a result of the drug alone. In most cases there was a decrease in temperature, some returning to normal. The remission of distressing symptoms suggests the possible use of streptomycin as a palliative treatment.

In 2 cases treated by mouth, one case did not improve appreciably and the other did not respond as well as those having intramuscular injections.

All other changes were inconsequential or negative.

SUMARIO

La Estreptomicina en la Enteritis Tuberculosa

Es todavía demasiado temprano y el material demasiado escaso para sacar conclusiones definitivas acerca del resultado de la estreptomicinoterapia en la enteritis tuberculosa.

Hubo ciertos resultados favorables constantes, o sean, sucintamente los siguientes: una sensación mayor de bienestar; desaparición casi completa de la anorexia, dolor y malestar abdominales en término de tres a diez días de la iniciación del tratamiento; desaparición de la diarrea por lo general dentro de dos semanas; en general mejoramiento apenas leve a moderado de los signos roentgenológicos (presentes en la mayoría de los casos); notable aumento de peso en 10 casos y mejoría del estado general en éstos. Un enfermo mejoró lo suficiente para permitir una operación pulmonar con éxito; en algunos casos disminuyó el esputo, si bien ninguno se negativó exclusivamente con la medicación; y en la mayor parte bajó la temperatura, volviendo en algunos a lo normal. La remisión de los síntomas molestos sugiere el posible empleo de la estreptomicina como tratamiento paliativo.

De 2 casos tratados por vía bucal, uno no mejoró apreciablemente y el otro no respondió tan bien como los que recibieron inyecciones intramusculares.

Los otros modificaciones no fueron de importancia.

DISCUSSIONS¹

An Antibiotic Precursor of Streptomycin

EUGENE C. DE SAVITSCH²

The use of antibiotics in tuberculosis is by no means new. A wide variety of substances have been used from the extracts of aspergillus and other molds, to the use of higher bacteria, with enthusiastic reports from test tube, animal and even clinical observations.

Some years ago the late Dr. Henry Sewall and I were impressed by the *in vitro* antagonism between the tubercle bacillus and an acid-fast saprophyte, the smegma bacillus. *In vivo* experiments in guinea pigs likewise demonstrated that smegma bacilli when injected simultaneously with virulent tubercle bacilli perceptibly retarded the development of the disease. In fact, in a certain number of cases, no evidence of macroscopic tuberculosis could be detected. If the smegma bacilli were injected into guinea pigs prior to the infection with tubercle bacilli, no such protection was noted. In more resistant animals, such as rabbits, the survival time of smegma-protected animals compared favorably with the controls.

In the attempt to isolate the therapeutic or immunizing fraction of the smegma bacillus a tuberculin-like substance, which we termed "smegmin," was prepared on Long's non-protein medium and tested on a large series of guinea pigs. The preparation exercised some therapeutic effect which only occasionally proved to be striking.

In summarizing the results of our work which covered a decade and in the course of which several thousand experimental animals were used, it was apparent to us that such favorable results as were noted, were, with rare exceptions, essentially retarding rather than clear-cut bactericidal action. In this respect the smegma bacillus appears to resemble that which is now being reported with the use of streptomycin.

Several years after the initiation of our studies, Fleming and Waksman isolated the long awaited antibiotic which from all indications merits serious trial by competent clinicians.

Toxic Effects of Streptomycin on the Eighth Nerve

JOHN S. CHASE³

Audiograms showed that in the majority of our cases there was no appreciable loss in the hearing of most patients under treatment with streptomycin.

A comparison of audiograms before and during treatment, and a comparison between the audiograms during treatment and after streptomycin was discontinued were presented. A comparison of 500 audiograms on 150 patients shows 94 cases of improvement during and after treatment, and 130 with no change; 18 with slight decrease in hearing.

The vestibular function is, however, definitely affected by streptomycin. In 18 patients receiving 2 g. or more daily for ninety days there were 15 who lost the vestibular response during treatment and 3 did not. Of 26 receiving one gram intramuscularly for

¹ Presented before the Medical Section, as part of the symposium on *Antibiotics and Chemotherapy in Tuberculosis*, at the 43rd annual meeting of the National Tuberculosis Association, San Francisco, California, June 18, 1947.

² Georgetown University School of Medicine, Washington, D. C.

³ Veterans Administration Hospital, San Fernando, California.

ninety days, 3 lost their caloric response during treatment and 7 after; 16 maintained their caloric response. Of 10 patients receiving one-half gram, there has been no loss of caloric response within three months. In 18 patients given 0.2 g. daily by aerosol or atomizer alone, no loss of caloric response has been found within three months.

The vestibular disturbance is also manifested by vertigo on moving the head, ataxia and dizziness. Of 35 patients taking 2 g. or more for ninety days with a normal Romberg to start, 10 were unable to walk with their eyes closed at the second month of treatment, 11 more were unable to walk with their eyes closed at the end of three months' treatment.

Compensation for this loss of vestibular function is eventually learned by the patient, enabling him to walk with his eyes open without steadying himself and gradually there is an improvement in walking in the dark, or with his eyes closed. It is believed that a systematic course of instruction in compensating for this vestibular loss would materially shorten the duration of this disability.

Tuberculous Ulcers of the Tongue

Three Cases

ARNOLD SHAMASKIN⁴

Case 1: W. P., a white man, age 52, with a predominantly productive quiescent pulmonary lesion, was treated for tuberculous ulcers of the tongue with intramuscular injections of 2.0 g. of streptomycin per day. His tongue lesions were present for approximately six months. The ulcers were completely healed by the end of sixty days of treatment and have remained healed since then, a period of three months. Treatment was continued for two months after the ulcers healed.

Case 2: L. H., a white man, age 57, with a predominantly productive pulmonary lesion, was treated for tuberculous ulcerations of the tongue with topical applications of 0.5 g. of streptomycin per day for thirty days, following which, due to unsatisfactory progress, therapy was changed to intramuscular injections of 2.0 g. per day. His tongue lesions were of approximately two years' duration. The ulcers were very much improved after 100 days of treatment. Since then the ulcer on the dorsum of the tongue, which is the oldest, has relapsed and is now almost the same size as when treatment was begun. There has been no relapse in the other ulcers and the patient has remained almost free from local symptoms.

Case 3: J. B., a white man, age 59, with an extensive progressive exudative bilateral pulmonary lesion, received topical applications of 0.5 g. of streptomycin and intramuscular injections of 2 g. per day, for his tongue lesions which were of five years' duration. His general condition was poor. He was given streptomycin as a palliative measure to see what effect, if any, the drug may have on a case of this type. The ulcers did not respond to treatment. His general condition continued to deteriorate. Streptomycin therapy was abandoned after sixty days.

The lesions in the first case were only six months old. They were completely healed in less than sixty days. One of the ulcers in the second case was two years old. This lesion was greatly improved objectively and subjectively at first but had partly relapsed by the

⁴ U. S. Veterans Hospital, Hines, Illinois.

end of 120 days of treatment. In the third case, the ulcers were five years old. They were not essentially affected by streptomycin.

Although there were in these 3 cases such variables as general condition of the patient and extent of the lesions, one wonders what rôle, if any, the age of the tongue lesions played in their susceptibility to the effects of streptomycin. Is it the same in the case of tongue tuberculosis as it is in pulmonary tuberculosis, namely: the older the lesions the more fibrosis and the less is the effect of streptomycin on it?

Tuberculous Meningitis

A 58-year-old colored man died after sixty-four days of streptomycin treatment for tuberculous meningitis and came to autopsy.

A section of the meninges and adjacent brain tissue revealed a granulomatous process with extensive necrosis. The cellular reaction consisted mostly of mononuclear cells, round cells, an occasional eosinophil and a few polynuclears. In the spleen multiple necrotizing tubercles were noted. The epithelioid reaction around the periphery was represented only by a few layers of cells. There were very few giant cells. We could not find in this case any evidence of healing.

Streptomycin with Intracutaneous Tuberculin-Vitamin Dosage

F. MAURICE McPHERDAN¹

There are clearly two major problems in the effective use of streptomycin against tuberculosis: first, the rapidity with which the organisms develop fastness against the drug and, second, the toxic side-effects. These will chiefly determine the method of dosage.

It has been brought out that fastness may become evident as early as the thirtieth day. From the laboratory we need to know what physical conditions measurable *in vitro* affect this. (1) If organisms are subjected very briefly to the higher blood level concentrations of streptomycin and, then, washed rapidly and injected into guinea pigs, are they more or less pathogenic than organisms subjected to lower blood level concentrations for much longer periods and, then, washed and similarly cultured? Stated otherwise, within what limits is the antibacterial action of streptomycin purely a matter of microgram-minutes? (2) Do the readily measurable and readily dialysable normal blood components, such as amino acids, glucose and vitamins, influence the antibacterial effect of streptomycin? This is particularly important with reference to thick-walled cavities and old infiltrations. (3) Do irritants, such as aleuronat, that produce leucocytes affect the dose of streptomycin that protects guinea pigs against tuberculosis? (4) Since (a) tuberculosis in guinea pigs predisposes to scurvy, (b) ascorbic acid is antiscorbutic, and (c) ascorbic acid stimulates phagocytic activity, study of the interrelation of these factors might throw light on the mechanism of streptomycin's action.

These problems are intimately related to the matter of clinical dosage and to the emphasis on toxic side-effects brought out in the reports of Doctor Hinshaw, of Doctor McDermott and of Doctor Barnwell. The prospect of impairment of vestibular function must be weighed against the established usefulness of streptomycin, which is decisive in the prognosis of many cases. For some, as in the case of pregnancy and tuberculosis cited below, 20 g. of streptomycin given subcutaneously, together with tuberculin, vitamins

¹The Germantown Dispensary and Hospital, East Wister Street, Germantown, Philadelphia, Pennsylvania.

and streptomycin intracutaneously, averted an almost certain fatality. (This combined intracutaneous method has been used in all our cases.) Likewise, (*Group A*—17 cases), when streptomycin was given at the induction of pneumothorax for six to twenty days, with a total rarely exceeding 10 to 20 g., pleural thickening and effusion were trivial or completely absent, fever was terminated and hospitalization shortened; thus the patient's outlook was abruptly altered and, in some, indicated surgery was obviated. Furthermore, these brief dosages fall short both of the minimum reported period for the development of drug fastness, and of the usual time within which occurs impairment of vestibular function. When streptomycin is available to those who are familiar with the standard rest and collapse treatment, there will be occasions clearly calling for a brief period of streptomycin treatment at least as often as there will be cases that can dispense with its use throughout the course of their treatment.

Group B: In 2 patients there was extensive pulmonary disease *ante-partum*. In one with moderately advanced disease involving the upper third of both lungs, in the eighth month of pregnancy, fever ranged to 103°F.; the patient was exhausted, anorexia marked, sleep poor, weight 108 lbs., down from 124 lbs. before pregnancy. The patient was so ill that it was thought she might not survive until delivery. During fever that had already lasted over five weeks she was given intracutaneously combined streptomycin, tuberculin and vitamins, and also given subcutaneously 2 g. streptomycin a day for five days. The temperature, which had been constantly elevated for over five weeks, became normal within five days. The intracutaneous administration alone was continued until delivery, nineteen days later. The patient was delivered November 24, and returned to the Research Department November 25 with a temperature rise to 99.3°F.; then, on November 26, to 102.2°F. At this point, together with streptomycin, tuberculin and vitamins given intracutaneously, 2 g. streptomycin were given daily subcutaneously for five days; the temperature again reached normal in forty-eight hours. The intracutaneous administrations were continued thenceforward, and the patient was discharged December 31. She has remained clinically well and free of fever, gaining weight to 129 lbs. There is no cough and no sputum. The lesion is sharply decreased.

The second patient was markedly underweight, with far advanced tuberculosis throughout the left lung and the upper third of the right. The lesion being clearly unstable, she was kept in bed *ante-partum*, without other treatment. On the eighth day *post-partum* the temperature began to rise, and reached 102.4°F. at the fourteenth day. There was no gynecological abnormality to account for this. On the fourteenth day *post-partum* the patient was returned to the Research Department, and treatment with streptomycin and intracutaneous injection of tuberculin and vitamins were begun, with 2 g. streptomycin subcutaneously daily. The temperature rose again to 99.3°F.; on the seventh day of treatment it returned to normal and has remained so. Streptomycin was continued in the amount of 2 g. daily for eighteen days. The patient was discharged and has been well at home since, returning every five days for intracutaneous injections of streptomycin, tuberculin and vitamins. The lesion is becoming sharper and more linear.

Group C: These patients present thick-walled chronic cavities known to have been established over months or years. These have been treated with subcutaneous streptomycin and intracutaneous injections of streptomycin, tuberculin and vitamins. In many, sharp improvement, contraction of thick "avascular" cavity walls, as shown by X-ray evidence, has been observed within one to two weeks after institution of treatment.

DISCUSSIONS

In some of these patients with indolent, old, dense lesions and with little or no fever, the concentrations used intracutaneously have varied widely: (1) streptomycin ranging from 10 units to 100,000 units per cc.; (2) tuberculin, ranging from first strength PPD to a dilution of 1:10,000,000. When streptomycin is given at the same time subcutaneously, concentrations of PPD up to 1:10 are effective in a very few patients, but the very much weaker dilutions of 1:10,000,000 to not more than 1:10,000 of the first strength PPD are both safer and effective. It cannot be too strongly emphasized that the addition of vitamins, even in the apparently minute dosage here reported, profoundly modifies the effect of the tuberculin reaction, and of the combined streptomycin-tuberculin reaction, not only in sharply altered edema and redness in the skin, but also in the effect on the pulmonary lesion.

For brevity, *sodium ascorbate* may be instanced. It appears to be the most generally useful vitamin for use in combination with streptomycin and tuberculin in the same intracutaneous bleb. It is made daily, diluted from a 250 mg. per cc. solution to the solutions used.

- (1) 0.2 mg. per cc., a 1:1,000 dilution of the basic strength. This is rarely used.
- (2) 20 micrograms per cc. This is usually the strongest concentration used.
- (3) 0.2 micrograms per cc. The most usual concentration.
- (4) 0.02 micrograms per cc. This is necessary for febrile patients and others who are strongly reactive to vitamin-streptomycin-tuberculin combinations.

A complete report is in preparation on the use of this method with other vitamins as well as with sodium ascorbate.

MULTIPLE PULMONARY CALCIFICATIONS¹

EDGAR ALSOP RILEY²

Pulmonary calcification falls into two large etiological groups, tuberculous and nontuberculous. Of all diseases, tuberculosis is the one which most frequently results in pulmonary calcification. Opie (1), who dissected many lungs showing calcification on X-ray examination, demonstrated that phleboliths, calcified emboli and other forms of calcification formed an insignificant proportion of calcific pulmonary lesions. There are about ten conditions which may cause pulmonary calcification. Many of these will not produce the picture of multiple bilateral discrete densities and may be mentioned only in passing.

Calcified emboli and thrombi are relatively rare. Multiple phleboliths may appear as parenchymal calcifications. Broncholiths, degenerating metastatic lesions and parasitic lung infestations are other unusual causes of pulmonary calcification. Ascaris has often been incriminated as a cause of pulmonary calcification, although Keller (2) could find no calcification in a series of patients with ascaris infection who had negative tuberculin skin tests. The theory of a metabolic disturbance resulting in the abnormal deposition of calcium in the lungs concerned several of the earlier writers on extensive pulmonary calcification. In 1925, Sutherland (3) after reviewing 60,000 chest films found 38 cases of multiple calcification and felt that the etiological factor was a metabolic anomaly causing the precipitation of calcium salt into the tissues from the blood. In rare instances a metabolic anomaly may be the etiological factor but only in cases of gross glandular or renal dysfunction. Pulmonary calcification in silicosis is discussed in an excellent review by Riemer (4). The calcification in silicosis is unique in that the lesions appear as large spherical nodules usually in the mediastinum with sharply demarcated calcified peripheries. The relation of this type of "eggshell" calcification to silicosis and tuberculosis is obscure. The X-ray appearance should not be confused with the type of calcification under discussion.

Multiple pulmonary calcification which more closely resembles the type under discussion is occasionally seen in association with mitral stenosis. The pathogenesis of calcification in this syndrome is obscure. Wells (5) felt that venous stasis favored osseous formation. Hurst *et al.* (6) postulated that the lesions developed due to breakdown and healing of multiple small stasis infarcts, sometimes resulting from severe passive congestion. Grishman and Kane (7) suggested as a possible cause the organization of transudate with calcification of these areas, facilitated by the presence of hemosiderin, with metaplasia into bony tissue. However, in 4 of 8 cases studied, there was no clinical evidence of cardiac failure, so it was felt that some factor other than vascular congestion must be involved. The difference in the X-ray appearance between calcified

¹ From the Medical Service, Fitzsimons General Hospital, Denver, Colorado.

² Captain, M.C., Letterman General Hospital, San Francisco, California.

hematogenous tuberculosis and the condition under study is discussed at some length by these authors. The salient X-ray features of this condition are:

- 1: Basal, bilateral distribution, not involving apices.
- 2: Mitral cardiac contour.
- 3: Absence of other evidence of tuberculosis.

Fungous infections have been implicated in the pathogenesis of pulmonary calcifications. *Coccidioides* (8) and *aspergillus* (9) have been suggested, but more important is the recent work on histoplasmosis. An excellent review of the subject by Christie and Peterson (10) summarized the studies done up to 1945. They stated that studies revealed "with monotonous regularity the fact that there is in a certain section of the United States a prevalence of pulmonary calcification far beyond what can be explained on a basis of tuberculosis as revealed by tuberculous skin testing." This high incidence of multiple calcification was also noted by Long and Stearns (11) who in a review of 53,400 chest films found that there was a 15 to 28 per cent prevalence of pulmonary calcifications in soldiers coming from the area bounded roughly by Fort Oglethorpe, Georgia; Jefferson Barracks, Missouri; Little Rock, Arkansas; and Columbus, Ohio, as compared with a 0 to 14 per cent prevalence elsewhere. (See figure 1.) It was not until the work of Palmer (12) that it was fully realized that a non-tuberculous agent, histoplasmosis, might be involved. Palmer (13) also showed a very definite geographic distribution of sensitivity to histoplasmin. In a series of nurses studied in eleven different cities he found a prevalence of 58 per cent sensitivity to histoplasmin in Kansas City, Missouri and a 4.8 per cent prevalence in Minneapolis. In general, the frequency of positive reactions decreased with increasing distance from the east central portion of the United States. It is interesting confirmatory evidence that half of the clinically proved cases of histoplasmosis have been reported from this area. A review by Palmer and Zwerling (14) of the chest films of the tuberculin-negative, histoplasmin-positive and the tuberculin-positive and histoplasmin-negative groups failed to reveal any clear-cut morphological difference, although it was felt that the total number of calcific deposits seemed greater in the histoplasmin-positive than in the tuberculin-positive persons. In 57 instances where hilar calcification measured more than 2 cm., 3 cases were tuberculin-positive, only 8 were positive to both antigens, 44 were negative to tuberculin and positive to histoplasmin and 2 failed to react to either skin test. The concept that tuberculosis is the only disease producing massive skin test. They can be differentiated by revision. There are many conditions other than tuberculosis which produce a miliary-like appearance on X-ray examination. They can be differentiated only by correlating the clinical course and findings. Austrian and Brown (15) list 21 diseases in which miliary disseminated densities occur in the lungs. However, none of these other conditions produces the X-ray appearance of multiple calcifications.

Miliary tuberculosis in the adult is usually considered a fulminating, rapidly progressive form of hematogenous tuberculosis. However, it is now generally

realized that in a small percentage of cases, miliary tuberculosis, due to factors still obscure, may go through the stages of resolution, healing and fibrosis to ultimate calcification. Opie and Anderson (16) felt that the presence of multiple calcifications indicated that the individual must have survived a severe tuberculous infection in childhood which caused few or no symptoms. Since then there have been many isolated reports of healed or healing miliary tuberculosis observed clinically. In a later article, Opie (17) makes two highly pertinent points: first, that the diagnosis of healed miliary tuberculosis can be made only with difficulty when multiple calcifications of the lungs is the first and sole evidence of an old healed tuberculous infection. The second point is that the dissemination, other than hematogenous, may be the result of healed childhood bronchogenic spread and that conclusive evidence as to the true method of dissemination may be wholly lacking.

Attempts have often been made to postulate the method of dissemination from the appearance of the calcific lesions on X-ray films. Crimm and Strayer (18) use the following classification:

(a) *Bronchogenic spread*

- 1) Lesions bilateral and asymmetrical
- 2) Lesions not so numerous.
- 3) Greater variation in size and shape

(b) *Hematogenous spread*

- 1) Lesions bilateral and symmetrical
- 2) Round areas of calcification more frequent than angular ones
- 3) Calcification present in hilar nodes

(c) *Mixed type of spread*

- 1) All types of lesions
- 2) Often masses of calcification
- 3) Lesions asymmetrical, bilateral, or unilateral

In a later article, Mayoral (19) points out that with a hematogenous spread there is usually no other demonstrable pathological change in the lung fields nor a focus from which bronchogenic spread can occur.

That it is extremely difficult to differentiate between the two types of tuberculosis, both clinically and morphologically, has been brought out in a series of articles by Miller (20), Pinner (21) and Rubin (22). These authors emphasize that, after a number of hematogenous foci coalesce and rupture into an alveolus bronchogenic seeding will occur, and that pure hematogenous tuberculosis is encountered only early in the course of the disease. Pinner makes the important points that hematogenous seeding does not have to be symmetrical, that it may be denser in certain areas of the lung than others and that it may lead to the development of a single focus anywhere in the pulmonary parenchyma.

The distribution of the hematogenous lesions will naturally depend upon the site of the focus from which the bacilli enter the blood-stream. Pulmonary

hematogenous dissemination occurs by either a rupture into the greater circulation (the bronchial arteries) or into the lesser circulation (the pulmonary artery). Rupture into an artery of either circulation will involve only that portion of the lung supplied by the vessel so that only a portion of the lung field may be involved. According to Rubin, rupture into the greater circulation will produce a uniform distribution of tubercles with no relation to the arborization of the tracheobronchial tree and with usually no involvement of the hilar nodes. On the other hand, rupture into the lesser circulation favors the development of tubercles in the alveoli, the lesions being larger than miliary tubercles, irregular in acinar or grape-like clusters and frequently confused with the results of bronchogenic dissemination. Rubin feels that in the absence of gross cavitating disease, without a history of hemorrhage or an acute pulmonary episode at some previous time, the seeding probably has occurred through the lesser circulation. The clinical course is extremely important in differentiating the method of spread, and Pinner has observed, "the chief clinical distinction from bronchogenic spread is that the whole natural course of the disease from seeding to healing may be without a single symptom."

How such extensive dissemination can occur without any elicitable clinical history in most instances is a perplexing problem. Mayoral puts forth two hypotheses:

- (a) That the seeding appears before the individual is sensitized and can resist the infection without clinical manifestation.
- (b) That seeding may occur from a newly reactivated lesion which was inactive long enough so that the tissues had become desensitized.

It is generally felt that the first hypothesis is more correct. It is true that individuals once sensitized to the tubercle bacillus may lose their sensitivity, but in the adult this is rare. Crimm and Short (23), in a study of 1,200 positive reactions with pulmonary calcifications, found that over a two to three-year period only 14 reverted to a state of negativity. Dahlstrom (24) found that, out of 1,000 cases with a 3+ skin reaction, only 0.4 per cent became negative, but that the incidence of reversion rose in direct proportion to the weakness of the skin reactions. The great majority of the unstable reactors were children. It is now generally believed that the initial infection with the tubercle bacillus produces sensitivity. However, this takes time to develop and an early post-primary hematogenous or bronchogenic dissemination conceivably can occur before allergy develops. Sweany (25) divides multiple tuberculous pulmonary calcifications into five different pathogenic groups, but his classification is complicated and difficult to understand.

Attempts to explain the method of dissemination on the basis of autopsied material have been almost as unsatisfactory as clinical and X-ray studies. Cases of multiple pulmonary calcification examined at autopsy have been reported only rarely. Geever (26) reported 2 cases of multiple pulmonary calcification with extensive bilateral hilar node involvement but with no lesions present in the liver or spleen. On section, these lesions showed caseation with

calcification and ossification. The author believed these 2 cases represented a primary type of infection occurring in infancy and proceeding to calcification. Terplan (27) reported 2 similar cases. Both cases revealed extensive calcification of the hilar nodes bilaterally but only one showed extrapulmonary tuberculous lesions. The lesions in this case showed various stages of calcification and the difference in ages seemed to indicate several episodes of hematogenous spread, possibly from some involved mesenteric nodes which showed caseation but no calcification. From the histological sections, the pathogenetic relationship between these calcified nodules could not be determined. Because of the symmetrical distribution and extrapulmonary involvement, hematogenous dissemination was thought to be the mechanism of spread. Terplan did not feel that the anatomical picture represented the end-stage of true miliary disease, the nodules being larger than miliary, measuring 1 to 3 mm. in diameter, but rather the result of repeated, clinically harmless, hematogenous seedings.

Forty-seven cases of multiple pulmonary calcification studied at Fitzsimons General Hospital fell into five different groups: group A was made up of cases of long standing reinfection type tuberculosis; group B consisted of cases in which only a chest X-ray film was available; group C cases with X-ray films and partial clinical data; group D, cases with X-ray films and complete clinical data; and group E, cases which had come to autopsy.

Group A consists of 5 cases of pulmonary tuberculosis of approximately twenty years' duration. Since these cases are well documented, they provide a valuable basis of comparison with others in this series. All 5 gave a history of hemoptysis on one or more occasions. Two cases presented definite clinical evidence of extrapulmonary hematogenous dissemination. In all, the calcifications were markedly irregular in shape and distribution, varying in size from 2 to 15 mm. The lesions appeared to be more dense, numerous and larger throughout the upper half of the lung fields. In 4 of the 5 cases, the lesions, particularly in the lower halves of the lungs, morphologically resembled those associated with bronchogenic spread. In addition to this type there were others occasionally present which were round and discrete, measuring 1 to 3 mm. in diameter, the kind usually considered typical of hematogenous seeding. All 5 cases showed marked secondary intrathoracic changes, such as tracheal deviation, mediastinal retraction, contraction of the intercostal spaces and compensatory emphysema.

Unfortunately, in this group we have been unable to obtain X-ray examinations showing the natural course of the disease to calcification. It can be assumed that the great majority of these calcified lesions have resulted from hemoptoic bronchogenic dissemination. A few individual lesions may have resulted from hematogenous spread. This type, however, does not seem to be especially predominant in the 2 cases with known extrapulmonary tuberculosis. In this study, pleural and pericardial adhesions, pleuritic changes and any marked diaphragmatic irregularities have been regarded as secondary to an old tuberculous infection.

Group B consists of 3 cases and group C consists of 11 cases.

From a study of this latter group it became readily apparent that little attempt was made to correlate X-ray and clinical diagnoses. This is especially true in 3 cases which showed no clinical evidence to support the X-ray diagnoses of coccidioides, aspergillus and multiple phleboliths. In 6 of these 11 cases the calcified lesions were wholly ignored in the clinical diagnosis. It is of interest that 2 cases were given certificates of disability discharge on the basis of psychiatric disorders, one because of anxiety hysteria and the second because of severe psychoneurosis. Three other cases were given certificates of disability discharge because of chest symptoms sufficiently severe to make these soldiers unfit for military service. The chest X-ray films of these 10 cases presented a picture varied in detail but with a pronounced total similarity. Occasionally the calcifications appeared to be superimposed upon bronchial shadows. This was true regardless of the type of lesion, but there was no way of confirming the anatomical relationships without stereoscopic films, which were not available. Group D consists of 26 cases. It is of interest that the pulmonary calcifications in the patient with well established evidence of mitral stenosis, case 38, were in no way different from the calcified lesions seen in many other cases in this series and did not fit into the pattern of calcifications associated with that cardiac condition. The lesions in this case were of the mixed type usually considered typical of hematogenous and bronchial spread. Bilateral hilar node calcification was present, which cannot be explained if the parenchymal lesions were on a noninfectious basis. This case probably does not fall into the category of lesions associated with mitral stenosis described previously. The only other case of rheumatic heart disease in this group was not associated with mitral stenosis.

Group E consists of 2 autopsied cases of multiple pulmonary calcifications. Unfortunately, no X-ray films are available in one of these cases to correlate with the pathological findings.

According to the autopsy report, examination of the first case, #46, was disappointing as no microscopic examination of the pulmonary lesions was made. The chest film was different from any other in the series because of the extensive fibrosis and large size of the lesions (figure 2). The left pleural space contained small amounts of straw-colored fluid. Bilateral thickening and scarring of the lower portion of the parietal pleura with similar involvement of the diaphragmatic pleura on the right side was reported. Numerous hard nodules were palpated throughout both lungs. Many of these nodules were subpleural in location with puckering of the overlying pleura. The tracheobronchial nodes were moderately enlarged and many were found to contain caseous areas while others had areas of calcification. Bacteriological studies were not done. This case showed no evidence of extrapulmonary tuberculosis. The final chest diagnoses were healed pulmonary tuberculosis and severe emphysema.

It is stated in the autopsy report that on examination of the lungs of the second case, #47, numerous calcified lesions, the largest measuring about 0.5 cm. in diameter, were found scattered throughout both lungs. When crushed, these lesions presented anthracotic pigmentation of the capsule and a dry yellowish-gray amorphous centre. Numerous sheets of adhesions were present overlying the posterior and the inferior surfaces of the

left lung. The left hilar lymph nodes showed anthracosis but no distinct tuberculosis. The nodes on the right side, in addition to anthracosis, showed calcification similar to that seen in the pulmonary lesions with areas of caseation. On microscopic examination the lung tissue appeared emphysematous. The calcific lesions were composed of central necrosis and amorphous zones with some secondary calcification. Around these lesions was a marginal deposition of hyalinized fibrous tissue in which lay occasionally radially arranged fibroblasts, epithelioid cells and Langhans giant cells. Anthracotic pigment was scattered in the periphery of the nodule. Sections of the hilar nodes showed several discrete nodules of fibrosis in an anthracotic background. The nodules were composed of central caseous or amorphous debris and had a laminated and hyalinized fibrous margin with a radial distribution of fibroblasts along the periphery. Bacteriological studies of the nodes and parenchymal lesions were not made. The slides were reexamined in an attempt to find some anatomical relationship between the lesions, the terminal bronchioles, the alveoli and the terminal vessels. However, all anatomical relationships had been lost, owing to the size of the calcified nodules and the distortion of the normal lung architecture, secondary to pulmonary edema, infarction and congestion. There was no evidence of any extrapulmonary tuberculosis. The pathological diagnosis of these lesions was calcinosis, pulmonary, miliary, bilateral, tuberculosis.

During the course of this study, it soon became apparent that, instead of solving the existing problems of the pathogenesis, etiology and pathological physiology of multiple pulmonary calcifications, fresh problems, not raised by other studies, arose. A discussion of these cases falls into three subdivisions—the etiology, the pathogenesis and the coexistent physiological and pulmonary complications. Five cases in group A are not included in this discussion, since the etiology and pathogenesis of the lesions in this group need no further elaboration. In view of the small number of cases included in this series, one of the most striking features was the geographical incidence (figure 1). Of 31 cases, where the birth state of the individual was known and where his childhood years were spent, 28 cases (90 per cent) came from that area found to be endemic for multiple pulmonary calcifications. This geographical distribution, with the state of Missouri as a centre, coincides almost exactly with the findings which have been discussed above.

It is obvious that this selectivity cannot be explained by any presently held concept of the etiology, pathogenesis or infectivity of tuberculosis. It must be agreed, especially in the tuberculin-negative individual, that some other etiological agent is responsible. A full discussion of the possibility of histoplasmosis being the causative factor has already been presented. Unfortunately the results of skin tests on the small number of persons in this series allows us to draw no etiological conclusions. Tuberculin skin tests, using purified protein derivative, were carried out on 17 individuals. Positive reactions to either first or second strengths were obtained in 15 cases, a negative reaction in one case (#39) and a questionable reaction in another. Eleven cases in this series were tested with histoplasmin 1:1000; 5 of the 11 cases reacted, including the one case with a questionable positive tuberculin skin test. Case 39 was negative to both antigens. No striking morphological differences in the chest lesions of the histoplasmin-negative and histoplasmin-positive reactors were

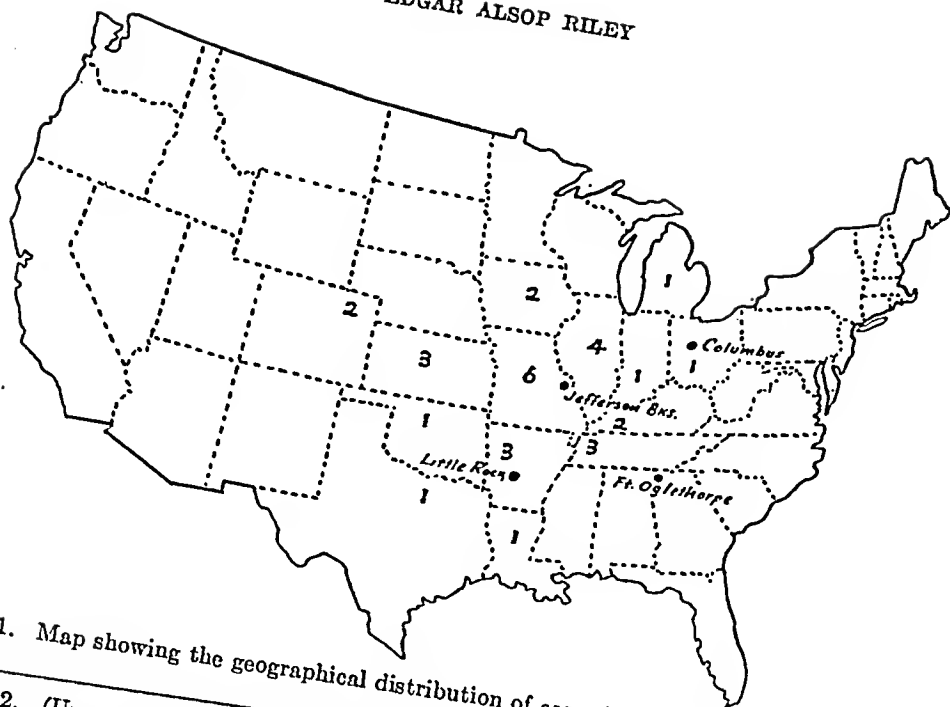


Fig. 1. Map showing the geographical distribution of cases included in this series.

Fig. 2. (Upper left) Case 46: a 56-year-old white male, admitted in coma, secondary to cerebral accident. EKG normal. Kahn 4-plus. Clinical diagnosis: tertiary syphilis, healed duodenal ulcer, prostatic hypertrophy. Note extensive fibrosis, marked bilateral hilar node calcification, and scattered calcified nodules.

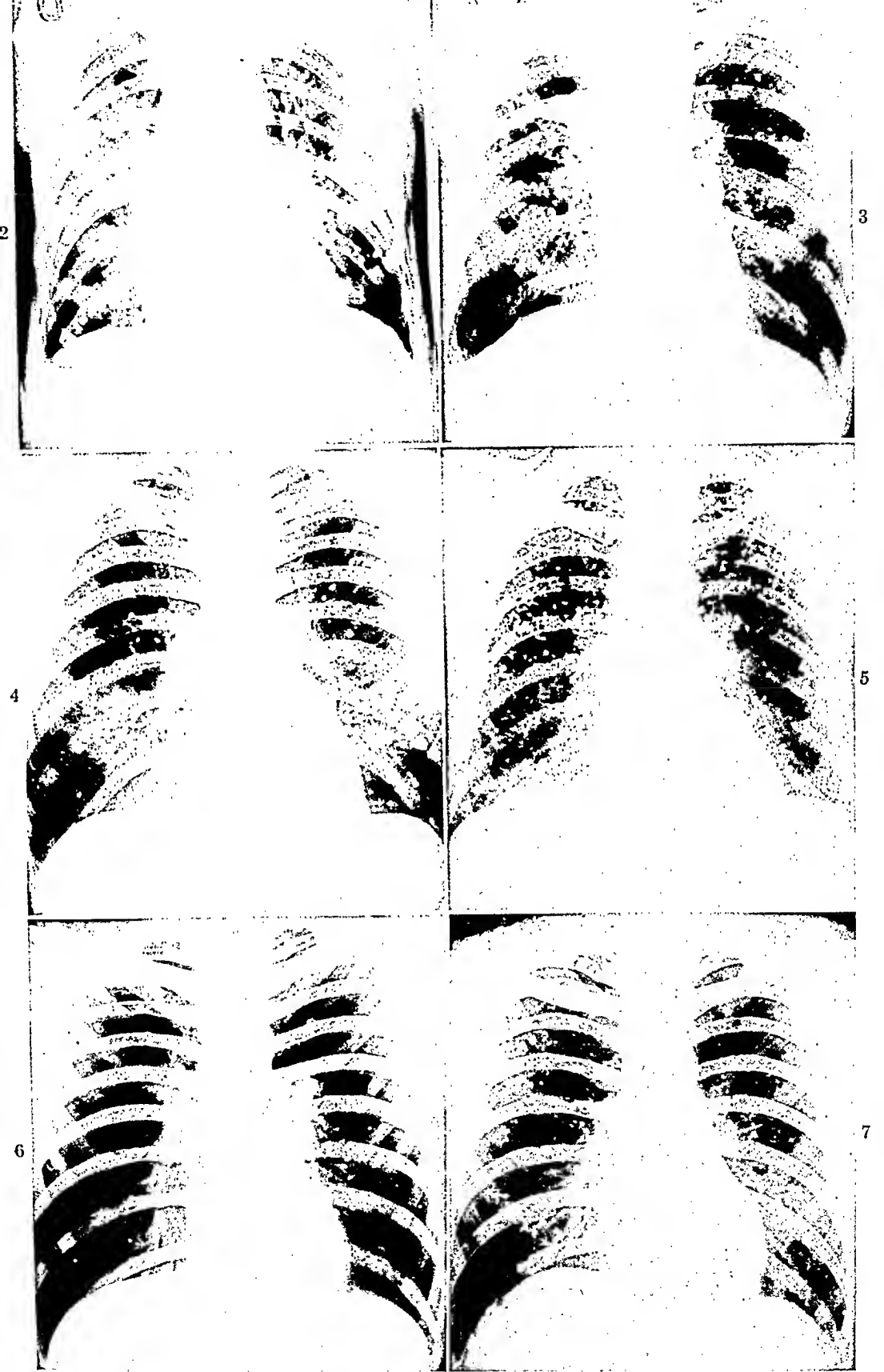
Fig. 3. (Upper right) Case 36: a 46-year-old white male with known tuberculosis since 1931. History of tuberculous contact. Vital capacity 69 per cent of normal. Note uniform bilateral distribution of the calcified lesions in association with active pulmonary tuberculosis.

Fig. 4. (Centre left) Case 31: a 38-year-old Kentucky born white male with sputum, cough, easy fatigue and dyspnea. No known history of tuberculous contact. PPD positive. Bronchoscopy normal; fungus cultures negative. Vital capacity 1,100 cc. Diagnosis: pulmonary tuberculosis, arrested; chronic catarrhal bronchitis; pulmonary fibrosis and emphysema; anxiety hysteria. Typical case showing basal predominance of the lesions with massive hilar node calcification. Both "bronchogenic" and "hematogenous" types of lesions are demonstrated on this X-ray.

Fig. 5. (Centre right) Case 39: a 49-year-old white Colorado born male, who was diagnosed pulmonary tuberculosis. Dyspnea and orthopnea. History of tuberculous contact. Histoplasmin and tuberculin skin tests negative. Vital capacity 43 per cent of normal. No history of any acute pulmonary episode. The lesions show a tendency to coalesce. Pathogenesis of the calcifications in this case is probably "mixed."

Fig. 6. (Lower left) Case 19. No clinical data available in this case, except that soldier was given a medical discharge with diagnosis of severe chronic suppurative bronchitis. Note the massive bilateral hilar node calcification and emphysematous appearance of the lung fields.

Fig. 7. (Lower right) Case 24: a 27-year-old white male born in Tennessee. Past history negative. Gastric cultures for tubercle bacilli negative. Histoplasmin and coccidioidin skin tests positive; second strength PPD questionable. No calcification of liver or spleen. Patient was asymptomatic and returned to full duty. Small widely disseminated discrete calcified nodules. Hilar node calcification is not prominent.



noted. Until more information is known concerning loss of sensitivity to histoplasmin, it cannot be said with certainty that in the nonreactors these lesions are not due to histoplasmosis. Nothing definite can be said about the 5 reactors, since the tuberculin skin reaction was concomitantly positive in 4 cases and questionably positive in one. This is only to be expected considering that the age group of the patients receiving both skin tests ranged from 21 to 54. For case 39, one of the most striking examples of massive calcification in this series, it would be reasonable to presume a nontuberculous etiology in view of the negative tuberculin test. It is difficult in this case to invoke the concept of loss of previously existing tuberculin allergy.

In the hope that the coexistence, with multiple calcifications, of active or old tuberculosis might lead to some etiological implication, the chest films in this series were carefully reviewed. There were 6 cases (14 per cent) of active tuberculosis and 19 cases (59 per cent) of old inactive tuberculosis, making a total number of 25 cases (59 per cent). The significance of this relatively high percentage cannot be wholly determined. It does seem higher than would be expected from comparative age groups selected at random. The incidence is apparently higher than that found in other reported series of pulmonary calcifications, in which the incidence of concomitant tuberculosis has not been statistically significant. It must be remembered, however, that the great majority of admissions to Fitzsimons General Hospital are cases of active tuberculosis. It is difficult to believe that there is any causal relationship between the development of an active tuberculous lesion and the calcifications, unless we postulate the breakdown of a partially calcified lesion which contains viable tubercle bacilli. It has been found, however, that the incidence of such calcified lesions containing viable bacilli is rare. Feldman and Baggenstross (28) in a study of 68 healed calcified foci could demonstrate tubercle bacilli by cultural methods and animal inoculation in only one instance. This work suggests that well calcified lesions are relatively harmless, although several studies suggest the opposite. Unfortunately in none of these 6 cases has it been possible to view the early development of the active lesion. The relative frequency in this series of fibrous pleurisies and changes considered secondary to tuberculosis of the pleura in conjunction with the presence of discrete round lesions is significant if we consider that such lesions result from hematogenous dissemination. Three cases gave definite histories of pleurisies with effusion. Any attempt to postulate an etiology of hematogenous tuberculosis in these cases is partially nullified by the fact that none demonstrated clinically any evidence of extrapulmonary tuberculosis. One case had extensive recent hematogenous tuberculosis with numerous extrapulmonary foci, suggesting a tuberculous etiological factor for the pulmonary calcifications. Flat abdominal plates in 5 cases demonstrated no calcifications in either liver or spleen, making a total of 7, including the 2 autopsied cases.

Realizing that these calcific lesions, if tuberculous, probably developed during childhood, it was hoped that a history of tuberculous contact would prove valuable. Thirty-three cases were investigated for possible contacts and a

contact history was found in 13 (39 per cent). In several cases, however, the intimacy of contact could not be ascertained. In 4 of these cases (12 per cent), no tuberculous stigmata were noted on X-ray films. This raises the possibility that in these cases, tuberculous contact during childhood might be correlated with the etiology of the calcified pulmonary lesions.

The finding in other series that personal histories were usually non-contributory was again substantiated. Eight cases (19 per cent) gave histories that might be associated with the development of the pulmonary lesions. These 8 cases include the patients mentioned with histories of pleurisy with effusion. The histories of several of these remaining cases are summarized in the accompanying case reports.

The description of the microscopic findings in the autopsied case is compatible with tuberculosis. However, there can always be some reasonable doubt unless the etiological agent is recovered. As has been demonstrated, calci-

TABLE 1

Comparison of two groups of cases of pulmonary calcification according to the presumed pathogenesis

	CRIMM AND STRAYER		RILEY	
	Cases	Per cent	Cases	Per cent
Bronchogenic.....	20	37	4	9
Mixed.....	17	32	13	31
Hematogenous.....	16	30	25	59
Total cases.....	53		42	

fication is not specific for tuberculosis, but results from the deposition of calcium salts under the proper physicochemical conditions into necrotic tissue.

Regardless of etiology it must be assumed that these lesions almost always result from a combination of hematogenous and bronchial dissemination. The ease and frequency with which hematogenous lesions may coalesce and rupture into alveoli with bronchial spread has been discussed. The converse is also true. To quote directly from Miller (29), "When the richness of the capillary network in the bronchial walls is considered, . . . it . . . assists in understanding how a localized infection in the wall of a bronchus or bronchiole may find its way through the epithelium and gain entrance, either into the vascular network in their walls or into a lymphatic and thus give rise to a hematogenous or to a lymphogenous extension of the infection." The schematic diagrams of the anatomical relationships within the primary lobule in Miller's book clearly show how rarely a pure form of either type of dissemination probably occurs.

Using the conventional classification, outlined by Crimm and Strayer (18) and also by Mayoral (19), it is interesting to compare this series with the series of calcifications studied by the former group. These findings are compared in table 1.

The percentage of "mixed" cases is almost identical in the two series, but

there is a marked difference in the number of the "hematogenous" and "bronchogenic" cases. This discrepancy is difficult to explain, since the same criteria for differentiating the two types of disseminations were employed. It has already been suggested that perhaps the best way of differentiating between the disseminative pathway is not by the X-ray appearance but by the clinical history. The 2 cases of the "bronchial type," cases 30 and 43, both gave histories suggestive of acute tuberculous episodes in the past. Of 9 cases of the "mixed type" of lesions with available past histories, 3 gave suggestive histories and in the 17 cases of the "hematogenous type" only 2 gave positive histories. Both of these cases were those of pleurisy with effusions.

Two aspects of the chest films should be stressed. In almost all cases of the "hematogenous type," the lesions showed a predominance for the mid and lower lung fields. This seemed to be real rather than apparent after allowing for the difference in lung volume at the apex and base and may be related to the relative avascularity of the apical areas. The "bronchial type" lesions were almost always confined to a single lobe or to the basal areas. Another interesting feature was the extensive variation noted in the calcification of the hilar nodes which seemed to have little relation to the size, number or distribution of the parenchymal lesions. Although there may be considerable difficulty in the interpretation of the extent of hilar calcification owing to the presence of other hilar structures, the differences were striking. High and his coworkers (30) suggest that "the observed differences in hilar calcification may represent significant differences in the pathogenesis of these two types of disseminated calcification." This observation is not born out by the findings in case 47 in which there was only unilateral involvement of the hilar nodes, although identical lesions were found uniformly distributed through both lung fields.

It has been emphasized by almost all workers that most patients with multiple pulmonary calcifications are without chest symptoms. Such has not been the case in this study. In 6 cases a diagnosis of suppurative or catarrhal bronchitis was made and in one of these, case 37, the clinical diagnosis was supported by bronchoscopic findings. Twenty-one cases (50 per cent) had chest symptoms. Fourteen of these cases had no parenchymal or pleural changes of sufficient severity, other than the calcified lesions and increased fibrous markings and hilar shadows which were noted on almost all of these chest plates, to explain their pulmonary complaints. Summary of these complaints is presented in table 2.

Emphysema and, in several cases, extensive calcification may be factors producing shortness of breath. Cough and sputum can be ascribed to a concomitant chronic bronchitis. Blood streaking is difficult to explain and, since this was only a presenting complaint, not noted during the period of hospitalization, perhaps should be discounted. The other symptoms can only be explained on a functional basis, and it is interesting that 4 patients in this group had psychiatric problems.

Vital capacity was found low in 5 dyspneic patients and ranged from approximately 25 to 80 per cent of normal variation. There was no correlation be-

tween dyspnea and the extent of calcification. Tests for respiratory reserve, such as recommended by Cournand *et al.* (31), were not done.

It was felt that pulmonary calcification might predispose to the development of cor pulmonale, secondary to changes in the pulmonary circulation. However, only one case (#42) developed frank right-sided failure. Several cases presented definite emphysematous changes but these cases were all in the older age group when emphysema could be expected to occur. Electrocardiograms taken on 12 patients showed no evidence of right axis deviation or right ventricular strain except in the one patient (case 38) with mitral stenosis.

This study once more illustrates that, until we have the opportunity by serial chest films to watch calcified lesions develop, heal and lay down calcium, and during this process recover the etiological agent, no etiological conclusions can

TABLE 2
Symptoms recorded in patients with multiple calcifications

COMPLAINT	NUMBER OF PATIENTS
Cough.....	11
Dyspnea.....	11
Sputum.....	6
Weakness.....	4
Easy fatigue.....	4
Chest pain.....	4
Streaking.....	3
Fever.....	2
Weight loss.....	2
Anorexia.....	2
Wheezing.....	1
Night sweats.....	1

be drawn. Clinically benign pulmonary hematogenous spreads do occur, as in one case following a prostatic massage, but only rarely are these spreads followed to the stage of calcification by the medical observer. No such case with complete follow-up and autopsy findings has been reported in the literature. Because of the varying factors discussed, the accurate pathogenesis of these lesions probably cannot be determined with certainty.

SUMMARY AND CONCLUSIONS

1. Forty-two cases of multiple pulmonary calcifications studied at Fitzsimons General Hospital are presented.
2. No further information as to the etiological agent has been obtained.
3. The pathogenesis of these lesions is probably hematogenous and bronchogenic and cannot be accurately determined from a study of the end-stages alone of the disseminating process.
4. This pulmonary condition may be accompanied by rather severe respiratory symptoms which cannot be wholly explained on an organic basis.

5. Until the opportunity is presented to watch such lesions from incipency to final calcification, and to recover the etiologial agent during the active phase, all discussion as to the etiologial factor and pathogenesis is purely speculative.

SUMARIO Y CONCLUSIONES

Policalcificación Pulmonar

1. Preséntanse 42 casos de calcificaciones pulmonares múltiples que fueron estudiados en el Hospital General Fitzsimons.
2. No se obtuvo nueva información en cuanto al agente etiológico.
3. La patogenia de estas lesiones es probablemente hematógena y broncógena, y no puede determinarse con exactitud por el estudio exclusivo de las fases terminales del proceso difusor.
4. Este estado pulmonar puede ir acompañado de síntomas bastante graves del aparato respiratorio que no pueden explicarse completamente desde el punto de vista orgánico.
5. Hasta que se presente ocasión de vigilar esas lesiones desde su incipencia hasta la calcificación final, y de encontrar el agente etiológico durante la fase activa, toda discusión relativa al factor causante y a la patogenia es puramente especulativa.

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MILIARY TUBERCULOSIS TREATED WITH STREPTOMYCIN

Report of Case with Necropsy Findings¹

FREDERICK H. TAYLOR² AND GEORGE G. SNIVELY³

Streptomycin has been shown to have a definite suppressive action on the clinical and pathological course of miliary tuberculosis as shown by clinical improvement and histological evidence of healing. The following case showed striking improvement under streptomycin therapy, but died as a result of concomitant involvement of the central nervous system.

CASE REPORT

A 30-year-old Negro male was first seen September 13, 1946. The onset of his illness was stated to have been in July, 1944, when, while in the South Pacific, he developed fever, diarrhea and abdominal cramps. Malarial parasites were reported in his blood smears, and *Endamoeba histolytica* cysts in his feces. He received courses of both atabrine and carbarsone, without marked improvement. In January, 1945, an "abscessed appendix" was removed. Sensations of fever, chills and occasional cramping pain in the lower part of the abdomen persisted until March, 1946. Careful study at that time revealed no organic disease. A chest X-ray film was reported as normal. In May, 1946, his fever returned, and he developed a dry, hacking cough. In June, 1946, he was restudied; another chest X-ray film was normal, as were numerous laboratory procedures. He ran a persistent elevation of temperature between 100° and 103° F. In August a painful nodule appeared on his right forearm, and a biopsy of this nodule showed "caseation and epithelioid cells but no giant cells or acid-fast bacilli." Sputum and gastric washings were repeatedly negative for acid-fast bacilli. Another roentgenogram of his chest in September, 1946 showed "miliary nodulations throughout both lungs" and the diagnosis of miliary tuberculosis was made.

Physical examination on admission revealed an acutely ill and markedly emaciated Negro male. His temperature was 103° F., respirations 28 and pulse 120 per minute. Blood pressure was 110/74 mm. Hg. Shotty cervical and inguinal lymph nodes were felt. Harsh breath sounds throughout both lung fields and moist râles following expiratory cough over both mid-lung fields anteriorly were detected. The right epididymis contained a firm, pea-sized nodule. The remainder of the physical examination was essentially normal. Admission laboratory studies showed the following: Hemoglobin, 14 g., white count, 7,600 with normal differential count, sedimentation rate (Westergren) 39 mm. per hour, negative blood Wassermann reaction, negative urine examination and negative patch test. Admission X-ray films of the chest (figure 1) showed "diffuse submiliary nodulation of both lung fields. The appearance is that of miliary tuberculosis." Shortly after admission the patient began a steady downhill course, becoming weaker, moderately dyspneic and disoriented, coughing much, but with little sputum, and with a temperature ranging between 101° and 103° F.

On October 20, 1946, he was started on streptomycin, 225,000 units intramuscularly every three hours, with a total dosage of 1.8 g. daily. A few days after treatment was started, he showed a suggestively positive bilateral Kernig's sign. The spinal fluid re-

¹ From the Veterans Administration Hospital, Columbia, South Carolina.

² 222 South Saluda Avenue, Columbia, South Carolina.

³ Waynesboro, Pennsylvania.

STREPTOMYCIN IN MILIARY TUBERCULOSIS

vealed a normal cell count, 50 mg. per cent protein, 784 mg. per cent chlorides; the colloidal gold curve and Wassermann tests were negative. The patient was given streptomycin intrathecally, 100,000 units daily between October 25 and October 31, and on November 1, 50,000 units intrathecally. In addition, he received intravenous fluids and general supportive therapy. Repeated laboratory studies throughout the patient's hospital course showed a white blood count fluctuating between 10,000 and 14,000 cells, with a shift to the left in the differential count, during the first month of his stay. This dropped during the last two months to range between 4,000 and 8,000 cells. His eosinophils were between 2 and 5 per cent during the second and third months of his stay.



FIG. 1

FIG. 1. Chest roentgenogram taken September 14, 1946, before starting streptomycin therapy. Miliary nodulations are seen throughout both lung fields.



FIG. 2

FIG. 2. Chest roentgenogram taken January 23, 1947, after three months of streptomycin therapy. There has been marked clearing of the miliary nodules.

His sedimentation rate ranged between 50 and 100 mm. per hour. His urine showed persistently low specific gravity, occasional traces of albumin and occasional red cells, white cells and granular casts. A urea clearance test on January 27, 1947 was 55 per cent, and repeated blood nonprotein nitrogen determinations were normal. Repeated examinations of urine, sputum and gastric washings were negative for acid-fast bacilli. Weekly audiograms during the period of streptomycin therapy remained within normal limits. During the first month of treatment his streptomycin blood level ranged about 5 micrograms per ml., but after the first month rose to between 10 and 20 micrograms per ml.

Chest examination at the onset of therapy was essentially unchanged from that done on admission. On November 20, the patient seemed clearer mentally and began to show steady clinical improvement. On December 12, 1946, examination of his chest revealed no change. Repetition of spinal fluid studies was contraindicated by decubitus ulcers over

the lumbar spine; these improved considerably under local therapy with tyrothricin, but never completely healed. His rectal temperature ranged between 99° and 102° F. during November and December, and between 99° and 101° F. during January, 1947. Repeated chest X-ray films showed a steady clearing of the lung fields, and on January 23, 1947, a chest roentgenogram showed marked clearing of both lungs (figure 2). Intermittent slight tinnitus and vertigo appeared on January 6, 1947, and continued through his hospital course. In the latter part of January, he developed intractable hiccoughs, which continued until the patient began to show evidence of increasing exhaustion. On January 31, his streptomycin was discontinued for three days, with the thought that the hiccoughs might be a toxic manifestation of the drug, but he showed no improvement and therapy was resumed. He gradually sank into a deep coma, developed Cheyne-Stokes respiration and expired quietly on February 8, 1947.

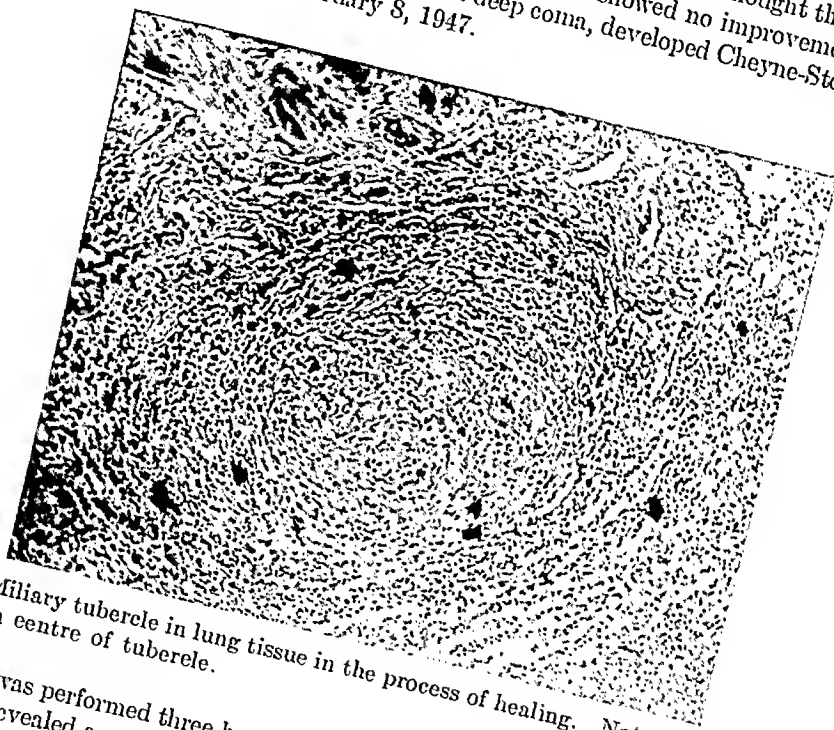


FIG. 3. Miliary tubercle in lung tissue in the process of healing. Note absence of caseation even in centre of tubercle.

Necropsy was performed three hours after death by one of us (G.G.S.). Examination of the brain revealed a moderately injected dura and a small amount of grayish exudate over the brain stem and basal cisterns. The brain weighed 1,220 g. In the right lobe of the cerebellum near the midline, a cavity, measuring 1.2 cm. in diameter and containing greenish-gray, soft, necrotic material, was found. No gross connection between this cavity and the subarachnoid space could be demonstrated. The lungs were markedly collapsed on opening the thorax, and a few easily broken adhesions found; the right lung 320 g. Both lungs showed a mottled pinkish-gray surface with occasional scattered white nodules averaging less than 1 mm. in diameter. The lungs were of firm, somewhat increased consistency and the cut surfaces were moderately congested. Uniformly salted throughout the parenchyma tiny pink-white nodules averaging perhaps 1 mm. in diameter were found; these blended very well in color with the parenchymal background and were better palpated as a slight roughening than seen. An ovoid cavity, measuring 2.4 by 1.0

STREPTOMYCIN IN MILIARY TUBERCULOSIS

cm., containing white, caseous material was found in the apex of the right lung. The pericardial sac contained some 150 ml. of clear fluid; its serosal surface was smooth and moderately injected. The remaining organs showed no grossly discernible abnormality. Microscopic sections taken through the portion of the cerebellum containing the cavity revealed an area of amorphous necrotic material, surrounded by a marginal zone of large, clear epithelioid cells. There was no sharp demarcation of this area from the normal brain tissue, and, as the diseased tissue shaded off into the normal white matter, a scattered infiltration of fibrocytes was noted, as well as giant cells of the Langhans type. Sections through the cavity of the right lung showed several large areas of caseous necrotic tissue surrounded by epithelioid cells, bordered in turn by a zone of small round cells. Many Langhans' giant cells were noted in these tubercles. In other sections of the lung occasional large tubercles with caseous centres were noted; these did not differ from the classical picture of tuberculosis. However, in the remaining lung there was evidence of a regressing process, with considerable connective tissue in the regions of tubercle formation (figure 3). This was particularly well demonstrated in sections stained for connective tissue. A marked and active fibroblastic response was noted, with occasional remnants of degenerated Langhans' giant cells and many degenerating epithelioid cells. Alveoli adjacent to the involved areas were small, appearing compressed, with an exaggerated lining membrane, the cells of which frequently tended to become almost cuboidal, and whose lumina contained occasional free histiocytes. There was a breaking down of some alveolar septa in the uninvolved lung sections with the production of the large air vesicles of moderate emphysema. Several small branches of the bronchial tree contained a cellular exudate composed of polymorphonuclear cells with an admixture of small round cells. Occasional tuberculous involvement of the bronchial wall and, in one portion, actual perforation of a small tubercle into the bronchial lumen were found. Microscopic examination of the remaining tissues was not remarkable, showing no evidence of tuberculosis. The anatomical diagnoses were: (1) bilateral pulmonary tuberculosis with miliary dissemination and with cavity formation in the right lung apex; (2) tuberculoma, right cerebellar lobe; and (3) tuberculous meningitis.

SUMMARY

A case of miliary tuberculosis treated with streptomycin is presented. The unusual features of this case are the marked clinical and radiological improvement of the tuberculous process and the remarkable histological evidence of healing of tubercles in the lung tissue.

SUMARIO

Granulía Tratada con Estreptomicina

Preséntase un caso de granulía tratado con estreptomicina. Las características inusitadas del caso consisten en la pronunciada mejoría clínica y radiológica del proceso tuberculoso y los notables signos histológicos de cicatrización de los tubérculos en el tejido pulmonar.

EDITORIAL

Streptomycin Treatment of Tuberculosis

Chemotherapy in tuberculosis is now an established resource. Persistent labors through years of failures and a succession of unfulfilled promises have at last borne fruit. The extensive investigations by Doctor Hinshaw and his collaborators, the Armed Services, the Veterans Administration and the institutions working under the auspices of the American Trudeau Society have demonstrated that streptomycin is an effective though limited contribution to tuberculosis therapy. The papers in the streptomycin symposium and the Report of the Subcommittee on Streptomycin of the American Trudeau Society published in this issue, and the forthcoming Report of the Council on Pharmacy and Chemistry of the American Medical Association have established its chief indications and effects. The physician treating tuberculosis must now not only evaluate the type and amount of rest and hygienic regimen required and the optimum time for instituting various types of collapse therapy or other surgical procedures, but he must also consider whether, when and how much streptomycin might be of value for each particular patient. Other antibiotics, and we hope other chemical agents, may supplement, and perhaps replace, streptomycin in clinical practice in the future, but some form of chemotherapy appears now to merit serious consideration in the therapeutic armamentarium of tuberculosis.

Great as has been the achievement revealed in these studies, much remains still to be learned. The chemical structure of streptomycin has been disclosed, its synthesis remains for the future. Improvements in production, purification and purveying should lead not only to further lowering of cost but to greater purity and effectiveness and lower toxicity of the product. Half-a-dozen modifications of streptomycin, the chloride, sulfate, phosphate, and calcium salt, dihydrostreptomycin, streptomycin B, streptomycin II, have been described, but better products must be sought further. Methods of chemical assay have been recently introduced but simpler, more precise procedures are desired. The dilution and plate methods of bio-assay in general use could also stand further study and improvement.

Little is yet known regarding the mechanism of action of streptomycin even in the test tube. What does it do to affect the metabolic or reproductive functions of the tubercle bacillus? Do high concentrations have bactericidal as well as bacteriostatic effects? Would concentrations too low for complete bacteriostasis still retard the development of the organism? Might still lower concentrations, on the other hand, stimulate increased activity and the multiplication of the tubercle bacillus? Is there a period of delay after its addition to a culture before streptomycin inhibits the growth and multiplication of the tubercle bacillus? How long a time elapses after the agent is removed before the bacilli again begin to grow and reproduce.

Extensive animal experimentation has already been carried out on mice, rats, hamsters, guinea pigs, rabbits, cats, dogs and monkeys, but more must be learned

from further animal experimentation. Too little is still known regarding factors affecting absorption and the possibility of delaying such absorption, as has been accomplished with penicillin, thus securing more prolonged effects. The distribution of streptomycin in various tissues and fluids of the body following its administration requires further study. Much may be learned regarding the effect of this distribution of coupling streptomycin to other molecules or carriers, such as the trypan dyes, and the effect of the altered distribution, so obtained, on its therapeutic efficacy. The rate of excretion of streptomycin, and the factors affecting this excretion want more precise investigation. Only a few fragmentary studies are available regarding the minimum levels necessary to manifest therapeutic response and the maximum level beyond which improvement does not follow increased dosage, and the optimal dose, frequency and duration of treatment have still to be determined.

Minimal lethal doses have been calculated for a few species and small series of animals, but the relation of such dosage to body-weight or body-volume of the animal, and of other factors requires more precise analysis. Delayed toxic effects should also be studied in animals in order that the responsible factors may be recognized. The toxic effects of streptomycin may be due to impurities, to unnecessary side actions of active components of the drug which may eventually be eliminated or to the very nature of its antibacterial action. We have still to discover whether they are due to the peak concentrations, the average or the minimal levels of the agent, and whether they may be reduced by more or less frequent injections, shorter or interrupted courses of treatment. The possibilities of allergic sensitization and desensitization or treatment with anti-histamine or other drugs should certainly be investigated in animals.

Tubercle bacilli in the test tube and in experimental animals as well as in treated patients develop resistance against streptomycin. Methods for recognizing and measuring this resistance have yielded conflicting findings. We do not even know what the mechanism of resistance to streptomycin may be. Are rare resistant bacilli present in untreated patients? Are they the result of chance mutations or dissociation, or do they develop gradually by adaptation from more susceptible strains? May resistant forms actually grow faster in the presence of streptomycin? Under what condition may the survival and predominance of preëxisting resistant forms or the development of ability to resist streptomycin on the part of susceptible forms be accelerated or, more important, be delayed or prevented? Do concentration, frequency or duration of application of streptomycin affect the occurrence or time of appearance of resistant tubercle bacilli? May combined treatment with sulfones or other agents prevent their development?

Streptomycin has been of undoubted life-saving value in certain cases of tuberculosis. It has healed some lesions in patients whose other tuberculous processes continued to progress. Symptoms may be relieved, although the pathological process and pathogenic bacteria persist. Too many patients show no benefit at all from the treatment. Why is this? We do not even know, yet, the pathological basis for the differences in results obtained. Experiments are needed to

show what type of lesions and in what phase of development healing by fibrosis may be expected and when healing by resorption may result from the treatment. The location and age of the lesion seem more important than its extent or character. Mucous membrane ulcers appear to respond miraculously to streptomycin treatment. Serous membranes or closed cavities in the body appear less favorably disposed. Bladder ulcers usually remain refractory. Chronic draining sinuses from tuberculous lymphadenitis or bone or joint tuberculosis often close promptly; bronchopleural fistulae show less favorable behavior. Acute postoperative spreads may resolve under streptomycin treatment; it cannot always prevent their occurrence. Fresh, acute miliary disseminations may fade away and tuberculous meningitis show prolonged remissions, but only too often resistant forms or associated cerebral lesions appear with fatal outcome. Fever may fall and sputum diminish while X-ray films do not show changes in chronic fibrocaceous pulmonary lesions. These tentative generalizations are not without exception; but much more work, clinical and pathological, must be done before we can understand why they occur at all and what might be done to change them. The individuals who, in various institutions, have carried out these valuable studies on streptomycin are to be congratulated on the results which they have achieved. More support is needed for continued and expanded investigations, more extensive and critical laboratory experimentation and more extended and critical clinical evaluation of the results. Streptomycin has already helped many patients with tuberculosis. With greater knowledge it should help more.

EMIL BOGEN

BOOKS

GEORGES LE CARBOULEC: *La Spéléotomie. With a preface by A. Bernou. Pp. 183, G. Doin et Cie, 8 Place de l'Odeon, Paris (6e), 1945.*

By T. G. HEATON

The first chapter traces the usually unfavorable history of cavernostomy prior to the procedure employed by the author, and then describes the development of the operation he terms *spéléotomie* at Chateaubriant.

A series of 21 cases operated upon by the author is then presented in detail in the second chapter.

The third chapter describes the ideas developed by the author from his experience with regard to the healing of cavities. He holds that more than one mechanism acts to close cavities and tends to emphasize the importance of the formation of granulation tissue ("*bourgeonnement*") in the final healing of a cavity, whether this has been rendered atelectatic by apposition of its walls and closure of the drainage bronchus or not. The author discusses in a further chapter the accurate diagnosis of the lesions in the lung beneath the thoracoplasty and the localization of the cavities.

Technique of operation is detailed in the fifth chapter, followed by a description of postoperative care, including packing of the wound and subsequent cauterization. What differentiates *spéléotomie* as practiced by the author from cavity-opening operations done elsewhere, is the practice of careful and prolonged cauterization of all the tuberculous tissue in the saucerized cavity. The object of the cauterization is the destruction and elimination of all the caseous tissue in the walls and in the draining bronchi of the cavity.

Indications and limitations of the procedure are discussed in chapter 6. The operation is undertaken nearly always for the treatment of residual cavities following thoracoplasty done several months previously.

Operative results are presented in chapter 7. Of 21 cases operated upon, 2 are dead. One of these was blamed on too prolonged evipan anesthesia. The other operative death was due to air embolus. Ten of the survivors had the cavity operated upon as the sole lesion in either lung. Of these, 8 are considered completely cured. The other 2 were well on the way to cure at the time of writing. Duration of postoperative treatment in this group varied from five to eighteen months to cure.

A second group of 5 patients had, in addition to the opened cavity, caseous foci nearby, and accessible to treatment through the operative field. Four of these were completely cured, the fifth making good progress.

A third group of 3 patients had exacerbations of tuberculosis on the same side as the *spéléotomie* and at some distance from the wound. All, however, did well eventually.

The fourth group consists of only one patient who suffered an extension of of tuberculosis on the opposite side and who was given a poor prognosis.

The author concludes that *spéléotomie* for residual cavity after thoracoplasty, if the opening of the cavity is sufficiently wide and if the cauterization of its walls and bronchi is done methodically, makes possible the cure of cavities in cases in which surgical collapse therapy, with or without Monaldi aspiration, has failed.

The resulting scar and deformity may be considerable. Methods of minimizing these are discussed.

This book appears to this reviewer to constitute a real contribution to the definitive treatment of this most difficult group of cases—failures by other methods.

W. BERBLINGER: *Formen und Ursachen der Herzhypertrophie bei Lungentuberkulose*. Pp. 183, with 26 illustrations and 7 charts, Medizinischer Verlag Hans Huber, Bern, 1947, paper, Fr. 10.20.

By BRUNO GERSTL

At a time when cardiovascular changes in patients with pulmonary tuberculosis find increasing attention Berblinger's monograph should be welcome. It presents the results of an extensive and thorough study of cardiac changes, both gross and microscopic, on over 150 cases selected so that other conditions that may have influenced the cardiac picture were practically excluded.

The book is more inclusive than is indicated by its title. Detailed discussions of the various methods of determining separately hypertrophy of right and left heart; of the formulae by which the parts of the septum belonging to either ventricle may be calculated; and of the way of estimating hypertrophy in an otherwise atrophic heart will allow control studies. The muscular changes observed by Doctor Berblinger in other conditions, such as congenital heart disease and pituitary disturbances, furnished a basis for comparison.

Long standing cachexia, whether due to cancer or tuberculosis, was found not to alter the relative weight of right and left heart. But the proportion of total heart weight to body weight shifted in such cases. In many cases of pulmonary tuberculosis hypertrophy of the right ventricle was absent and the heart was frequently rather small, although considerable narrowing of the pulmonary vascular bed was demonstrable. On the other side, only half of the cases that did show right-sided hypertrophy could be explained on the basis of elimination of pulmonary vessels. Hence, functional narrowing of the precapillary vessels, possibly due to inflammatory processes in the surrounding lung parenchyma, are considered by the author as causative factor. The conclusion that hypertrophy of the right heart may occur early in patients with pulmonary tuberculosis but may escape detection by both roentgenographic and electrocardiographic examination and that thoracoplasty or phrenicectomy do not enhance hypertrophy due to tuberculous disease is of clinical importance. Doctor Berblinger's book will be a valuable reference volume for all concerned with cardiac physiology.

ARESKY AMORIM: *Tratamento cirúrgico da tuberculose pulmonar na grávida*. Prologuc by Luis Sayé. Pp. 217, with 82 figures, 1946, Editora Científica, Rua do Ouvidor, 145—Rio, paper.

By ARISTIDES A. MOLL

This beautifully printed and illustrated monograph deals with a problem which many physicians, and especially those working in tuberculosis, often face: What to do with the pregnant tuberculosis patient? The question is faced openly and courageously in order to come to a conclusion based on scientific experience. The advice is that tuberculous mothers can perfectly stand surgical treatment, and there is, as a rule, no need or excuse for abortive or anticonceptive measures. Pinard's dictum still retains its full force, "Treat the tuberculosis, and let pregnancy follow its course under supervision." It is recalled that Forlanini himself used this method in pregnancy cases. Kuthy and Lobmayer (1913) and Rist and Kindberg (1914) followed and extended the practice. By 1925, Léon Bernard stated that pneumothorax has restored to tuberculous women their fitness for child-bearing. The data presented in this book include dozens of cases embracing phrenicectomy, extrapleural pneumonolysis (which has many contraindications), thoracoplasty (perhaps the largest series so far reported), and even bilateral collapse therapy, these cases being among the few so far published. An earnest plea is made for organized protection for the tuberculous woman who becomes pregnant, in accordance with the example set by Buenos Aires and Paris.

HERNAN D. AGUILAR: *Asistencia de los Enfermos Tóracopulmonares*. Volume 1 of the *Biblioteca de la Enfermera de Cirugía*. Second considerably enlarged edition. Pp. 260, with 105 illustrations, Librería y Editorial "El Ateneo", Florida 340, Buenos Aires, 1946, paper.

By WILHELM SWIENTY

This little manual is a reference book for physicians and nurses who are interested in the treatment of chest diseases. It covers practically everything from the anatomical and physiological fundamentals, diagnosis and differential diagnosis of the more common surgical chest diseases to an exhaustive description of the different types of thoracic operations with suggestions for pre- and postoperative care. The chapter on postoperative care after thoracic surgery emphasizes the need for the much neglected correction of scoliosis and other deformities of the thorax. Every surgeon knows what a blessing and relief it is to be able to turn over the patient to a reliable and competent nurse after major thoracic surgery. It is one of the purposes of this book to make this possible. Excellent X-ray pictures and sketches accompany the text. Although written for nurses in its easy and pleasant reading, it is also recommended for the specialist.

WILLIAM F. PETERSEN: *Hippocratic Wisdom. A Modern Appreciation of Ancient Medical Science.* Pp. xix + 263, with many illustrations, 1946, Charles C Thomas, Springfield, Illinois, keratine, \$5.00.

By MAX PINNER

Along with numerous translations of the Hippocratic writings, the interpretative literature about Hippocrates is so voluminous, so contradictory and, in essence, so confusing, as to be remindful of biblical exegesis. Because classical experts have probably more frequently indulged in this mental exercise than have medical scientists, the apparent aim was all too often historical-linguistic rather than the elucidation of the Hippocratic teachings or the explanation of their significance. For some, Hippocrates is mainly a venerated historical curiosity with little if any relevance to present-day medicine; for others, he has become the representative of medical ideas of immortal value. Doctor Petersen obviously belongs in the latter group, but in a quite particular and admittedly subjective way. Doctor Petersen's primary aim is not an up-to-date and complete interpretation of Hippocrates, but a *post-hoc* demonstration of the extent to which Hippocrates saw and taught those problems and points of view that Doctor Petersen has done so much to reintroduce—with modern methods—into current medical thought. With profound respect for Hippocratic wisdom, Doctor Petersen uses it frankly for his own purposes. He does not only present certain parts of Hippocratic writings as necessary foundations for modern biological theory (and practice) but he strongly suggests what Hippocrates *might* have said had he had modern scientific tools at his disposal. It is, then, not astonishing that the area of agreement between Hippocrates and his latest interpreter is rather wide, particularly in the field of "meteorological medicine."

The most important single medical concept created in the last century is probably that of the dynamic constancy of the "inner milieu." Doctor Petersen, having himself contributed to this field of knowledge, has long since fought to gain proper recognition for those forces and their mediating mechanisms of the environment that periodically assault the serenity of the "inner milieu" and disturb it (that is, cause disease), at least in the more vulnerable individual. In this endeavor he has found about as much acceptance and recognition as any reformer (or heretic) in medical thought has ever received from his contemporary colleagues, established in the recognized school of thought. He now has summed, in this book, the intellectual support of a man (or men) whose conceptual respectability and fame are not easily challenged, just as he tried in a former book to demonstrate the human and historical applicability of his meteorological theory. As far as his present book is concerned, it takes probably the *rara avis*, who is an expert both in Greek linguistics and in scientific biology, to decide whether Doctor Petersen has written a new and acceptable interpretation of Hippocrates or whether he has interpreted *into* Hippocratic writings the fruits of his own medical observations. This reviewer cannot qualify for either type of expert knowledge. But he can say, and wishes to say so with emphasis, that anyone will read, with profound interest and sheer delight, Doctor Peter-

sen's book—that is, anyone who enjoys speculation and believes that, even in modern medicine, abstract thought and philosophizing have a legitimate, yes, even a constructive rôle.

ROGER G. BARKER, BEATRICE A. WRIGHT AND MOLLIE R. GONICK: *Adjustment to Physical Handicap and Illness: A Survey of the Social Psychology of Physique and Disability*. Pp. xi + 572, Social Science Research Council, 250 Park Avenue, New York 17, Bulletin 55, 1946, paper, \$2.00.

By ANN LEHMAN

From the title, the rehabilitation worker might expect to find answers to questions relating to the effects of physical disabilities on social behavior and personality. Because of the wide variations of the findings in the fields covered, he fails to obtain it.

The authors, however, point out in the Introduction that they are assembling and evaluating the existing literature on behavioral adjustments of disabled persons. In addition, they indicate problems for further investigation. The following areas are covered: unusual physical size, muscular strength, motor mobility, auditory impairments, tuberculosis, orthopedic disabilities, acute illness and employment of the handicapped.

A study on the relation between social behavior and personality and normal and pathological variations in physique was a happy selection by the authors for their first analysis. Appreciation of the behavior of the obese, the very tall, the very short and beautiful persons and the reactions of others to these characteristics is an easy approach to the later chapters on the effects of crippling, tuberculosis, impaired hearing and acute illness which make deeper changes on the personality.

As the readers of the REVIEW are primarily interested in tuberculosis, this review will concentrate on this aspect of the book.

Although the bibliography on tuberculosis enumerates 170 references from literature in English, German and French, the authors believe that only 10 present data in such a way that an evaluation of conclusions is possible. In addition, the authors review material where only the conclusions are reported and have analyzed the literature to cull the expressed opinions of 44 medical experts.

It is evident that authorities have never agreed on the behavior of persons with tuberculosis. The authors list the contradictory terms they found describing this behavior: "euphoric, depressed; increased sex urge, decreased sex urge; fearful, confident; intellectually alert, intellectually dull; anxious, unconcerned; extroverted, introverted; realistic acceptance of disease, rejection of disease, indifference to disease, malingering to continue treatment; self-centered, self-effacing; low vitality, drive; optimism, pessimism; guilt, hate; day-dreaming, sensitive to outside stimuli; anti-social, social; high strung, phlegmatic." With this to start with, the authors present their findings.

In the field of scientific research, Singeisen's study of Rorschach responses of tuberculous and cardiac patients with physically normal persons is the first covered. The author of the study considers that the findings reveal that the tuberculous are impulsive and unstable; with a large amount of frustrated effect which makes them discontented. The large number of anatomical responses show a preoccupation with bodily pathological processes that are higher than with hypochondriacal or anxiety cases.

The Maller Personality Sketches administered by Seidenfeld indicate a greater maladjustment of the tuberculous. The authors, however, do not believe such personality inventories can be interpreted in terms of standardizations based on healthy individuals, as the life situation of the sanatorium patient is radically different. A Bernreuter personality study found tuberculous patients introverted, more neurotic, less self-sufficient, more submissive, less self-confident and more sociable than normal subjects.

The authors review a study made by Strickland, Braceland and Gordon covering 75 clinical, psychiatric interviews with patients with active tuberculosis. They are interested particularly in the patients found euphoric. After studying them in greater detail, they conclude: "There were no cases of euphoria that were not tainted. None of them could be regarded as being euphoric as the result of the presence of tuberculosis." Their conclusion was that the most persistent mood of the tuberculous patient was one of apprehensive anxiety.

In analyzing the opinions of experts, the authors state that 19 of the 44 authors believe that there is no unique tuberculous behavior. Lawrason Brown, who surveyed the literature in 1933, is quoted: "Contradiction contradicts contradiction and the tuberculous patient is described as being anything between an insane criminal and a saint too ethereal for this mundane world."

In summarizing opinions on behavior, the authors agree that a great variety of behavior is exhibited by tuberculous persons and that some kinds are more frequently found than in normal persons such as anxiety, mild neuroticism, neurasthenia and discontent. Data on sex drive are inadequate and there seem to be data supporting a tentative hypothesis that tuberculosis may be associated with a slightly increased intellectual functioning.

Careful consideration is given to the psychological situation in which the tuberculous patient is placed in order to determine whether the situation itself causes the infectiousness and seriousness of the disease creates a frequent exclusion of the tuberculous behavior. The creation of a tuberculophobia by agencies publicizing arrested cases from safe vocational and social activities.

The authors point out a lack of fictional literature of personal documentation on tuberculosis. They indicate the need for studies reporting sanatorium life from the point of view of the patient, as well as the effects of sanatorium practices upon the patient and recovery rates. The authors recommend greater participation of the patient as an active agent in treatment procedures which would increase his feeling of self-competence.

In order to relieve the sanatorium patient from anxiety and emotional tension, the authors recommend that the sanatorium include educational, vocational

training and part-time work for as many patients as possible. This would change the psychological situation from one of conflict and frustration to one that provides elements of satisfaction.

The post-sanatorium situation is discussed with recommendations for systematic vocational training and temporary sheltered employment of the type offered by Papworth Village and Altro Workshop. This should be combined with general education to reduce the fear of tuberculosis which sets up unnecessary social and vocational barriers against the ex-tuberculous.

EDWARD W. HAYES: *Tuberculosis as It Comes and Goes*. Second Edition. With chapters by Laurence de Rycke. Pp. ix + 220, with 43 illustrations, Charles C Thomas, Publisher, Springfield, Illinois, 1947, cloth, \$3.75.

By JOHN D. STEELE

This is the second edition of this book, the first edition of which was published in 1943. It is written primarily for tuberculous patients. A chapter has been added in the second edition by Laurence de Rycke on "Suggestions to Patients;" otherwise the text is practically the same as that of the previous edition.

History, epidemiology, pathology and diagnosis are treated briefly and simply in the first third of the book. Controversial issues are explained simply. While issue might be taken by some physicians in regard to several of the explanations of the pathological aspects, it is doubtful whether further clarification of such issues would be of any great benefit to the patient-reader.

Some of the chapters on treatment are simple and avoid controversial subjects. The discussion of sanatorium *versus* home treatment is excellent as are the chapters on diet, climate and heliotherapy.

The chapters on collapse therapy are illustrated with diagrams accompanied by short case histories. Dogmatic statements are made in regard to the management of pneumothorax which will not be acceptable to many plithisiologists and which should not be read by patients in institutions where adherent lungs and relatively small pneumothorax pockets are not tolerated. The complications and limitations of various collapse procedures could well have been explained to better advantage.

Statements in regard to the use of drugs, including suggested dosages in the control of symptoms, seem particularly objectionable, as patients might conclude that they were being neglected unless they were receiving the same drugs as recommended by Doctor Hayes. Such statements belong in a medical text-book rather than in a book of this type.

Like many books written for the same purpose, this one will be most useful for the patients under the care of its author. It cannot be recommended, without qualification, for general distribution to tuberculous patients, in spite of many commendable features.

Books Received

- HOWARD T. BEHRMAN: *Dermatologic Clues to Internal Disease*. Pp. 165, with 118 illustrations, Grune & Stratton, New York, 1947, cloth, \$5.00.
- A. ALGEMEEN GEDEELTE: *Verslag. Over het jaar 1943 van den Geneeskundig Hoofddirecteur van de Volksgezondheid*. Pp. 150, with many tables, Verslagen en Mededeelingen, Betreffende de Volksgezondheid, September, 1946, paper.
- F. R. G. HEAF AND J. B. McDUGALL: *Rehabilitating the Tuberculous*. With a foreword by Her Grace the Duchess of Portland. Pp. xii + 142, with 20 illustrations, Faber and Faber Ltd., 24 Russell Square, London, 1947, cloth, 8s. 6d.
- ARCHIBALD REYNOLDS JUDD: *Diseases of the Chest. Diagnosis and Treatment*. Pp. xii + 608, with 140 illustrations, Philadelphia, F. A. Davis Company—Publishers, 1947, cloth, \$9.00.
- R. Y. KEERS AND B. G. RIGDEN: *Pulmonary Tuberculosis. A Handbook for Students and Practitioners. Second Edition*. With a foreword by F. H. Young. Pp. xvi + 277, with 124 illustrations, A William Wood Book, The Williams and Wilkins Company, Baltimore, 1946, cloth, \$5.00.
- GRACE M. LONGHURST: *Tuberculosis Nursing. Second Edition*. With the collaboration of N. Stanley Lincoln and Richmond Douglas. Pp. xii + 358, with 74 illustrations, Philadelphia, F. A. Davis Company—Publishers, 1947, cloth, \$3.50.
- LEWIS J. MOORMAN: *The American Sanatorium Association. A Brief Historical Sketch. Historical Series Number 3*, pp. 72, National Tuberculosis Association, New York, 1947, paper.
- ELI H. RUBIN: *Diseases of the Chest: With Emphasis on X-ray Diagnosis*. Pp. 685, with 355 illustrations (24 plates in color), W. B. Saunders Company, Philadelphia and London, 1947, cloth, \$12.00.
- HANNES SALMENKALLIO: *Die durch Knochen- und Gelenktuberkulose verursachte bleibende Arbeitsunfähigkeit in Finnland. Eine Statistische Studie*. Pp. 60, with 18 tables, Supplementum 1, *Annales Chirurgiae et Gynaecologiae Fenniae*, Helsinki, Vol. 36, 1947, paper.
- ERIK VON ROSEN: *Studien über die Lungendurchleuchtung in der Tuberkulosebekämpfung, ihre methodologische Eigenart im Vergleich zur Lungenradiographie und ihre praktische Brauchbarkeit und Zuverlässigkeit*. Pp. 245, C. W. K. Gleerup, Lund, Sweden, 1941.
- VII Congreso Pan-Americano de la Tuberculosis, Lima, Peru, 17-22 de Marzo de 1947. Pp. 563, Editora Medica Peruana S.A., Azangaro 906, Lima, Peru, 1947, paper.
- Industry, Tuberculosis, Silicosis and Compensation. A Symposium. Prepared by Committee on Tuberculosis in Industry of the National Tuberculosis Association and American Trudeau Society. Leroy U. Gardner, Editor. Published by National Tuberculosis Association, New York, 1947. Contributors: Paul Bamberger, Leopold Brahdry, Leroy U. Gardner, David Gould, L. E. Ham-

- lin, Herman E. Hilleboe, B. E. Kuechle, A. J. Lanza, Ada Chree Reid, O. A. Sander, W. P. Shepard, C. D. Selby, George Wright. Pp. 126, cloth.
- Le problème des tuberculoses atypiques. Étude clinique by R. Burnand, H. Jaeger, M. Amsler, F. Verrey and E. Martin. Étude anatomique by J. L. Nicod. Étude bactériologique by P. Hauduroy. Pp. 435, with 20 figures, Masson & Cie, Éditeurs, Paris, and F. Roth & Cie, Éditeurs, Lausanne, 1946, paper, 760 fr.
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AMERICAN TRUDEAU SOCIETY
Report of the Committee on Coöperation with the American Board of
Internal Medicine

Dr. J. Burns Amberson, *Chairman*
Dr. Robert G. Bloch
Dr. David A. Cooper
Dr. Sidney J. Shipman
Dr. Julius L. Wilson

In 1941, when Advisory Boards were appointed by the American Board of Internal Medicine, there was considerable discussion of the certification of specialists in tuberculosis who qualified after being certified in Internal Medicine. It was decided then that the time was not ripe to certify these specialists under any other designation. Since then, largely under the stimulus of the American Board of Internal Medicine, an increasing number of young physicians have taken formal training not only in tuberculosis but also in the general and closely related field of diseases of the chest. This field has become better defined because of important knowledge which has accumulated in recent years and can best be applied in practice by those who have qualified through training. The American Board of Internal Medicine at its last meeting decided therefore to change the designation of certification in tuberculosis to certification in Pulmonary Diseases. The fundamental policy of the Board remains unchanged; namely, a physician must first qualify by examination for certification in Internal Medicine, after which he may be certified in addition, after passing the examination, in Pulmonary Diseases.

The following were elected members of the Advisory Board for Pulmonary Diseases:

Dr. David A. Cooper
Dr. Donald S. King
Dr. J. Arthur Myers
Dr. Sidney J. Shipman
Dr. Julius L. Wilson

Your Committee is of the opinion that the present organization and policies of the American Board of Internal Medicine are sound and progressive and should receive the full support of all physicians committed to the improvement of standards of medical practice. Since the original functions of the Committee have been fulfilled, it would seem that the Committee should be discharged.

Report of Medical Advisory Committee on Health Education

Dr. Kirby S. Howlett, Jr., *Chairman*
Dr. William H. Oatway, Jr.
Dr. Arthur A. Pleyte

During the past year, the Medical Advisory Committee on Health Education has reviewed, prior to publication, manuscripts submitted by the Director of

¹ All of the committee reports published in this section were presented at the 42nd annual meeting of the American Trudeau Society, San Francisco, California, June 17, 1947.

Health Education of the National Tuberculosis Association as follows:
Dollars and Sense, 1947 educational insert for Seal Sale letters.
I Went to the Sanatorium.
Rest to Beat TB.

TB Facts (replaces *Plain Talk*).
Do You Know the Answer, quiz sheet on tuberculosis.

Your Town Is Having a Chest X-ray, tabloid picture story on tuberculosis.
Help Fight Tuberculosis.

What about Climate?

Visual Aids Unit #3:

A Message from Dorothy Maynor, motion picture.
Cheek Up on Your Chest, film-strip.

Get a Chest X-ray, audience guide.

Visual Aids Unit #4:

Time Out!, motion picture (former title *The Will To Do*).

In each instance general approval was expressed both on the basic idea and of material written. In most instances, however, a number of suggestions were made for the alteration of certain details.

In addition to suggestions pertaining to submitted manuscripts, several suggestions were also made as to somewhat different types of publicity by the use of radio and National magazines. These suggestions also were submitted to the NTA Director of Health Education for consideration.

Report of the Committee on Medical Information

Dr. Theodore L. Badger
 Dr. Maurice Campagna
 Dr. William G. Childress
 Dr. H. Dumont Clark
 Dr. John K. Deegan

Dr. Ezra Bridge, *Chairman*
 Dr. Edward P. Eglee
 Dr. John C. Ham
 Dr. L. H. Hetherington
 Dr. John C. Jones
 Dr. Carl Muschenheim
 Dr. D. E. Quinn

The Medical Information Committee of the American Trudeau Society furnishes articles with a medical slant for the BULLETIN of the National Tuberculosis Association. The members met this responsibility during the past year either by writing the articles themselves or by obtaining them from associates. Of the 20 articles submitted, 12 were written by members of the Committee and 8 by associates. The following were written by Committee members:

Chest X-rays for General Hospital Admissions—William G. Childress, M. D.
Overcoming the Danger of Infection in Hospitals and Sanatoria—William G. Childress, M.D.
How Best to Tell Him He Has Tuberculosis—John C. Ham, M.D.
Tuberculosis Case-finding and Control in Hospital Personnel—John C. Ham, M.D.

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- How Best to Tell Him He Has Tuberculosis*—L. H. Hetherington, N.D.
An Approach to Undergraduate Tuberculosis Teaching—L. H. Hetherington, M.D.
How Best to Hunt for Tubercle Bacilli—L. H. Hetherington, M.D.
The Future of Streptomycin—Carl Muschenheim, M.D.
When Is Tuberculosis Inactive?—Carl Muschenheim, M.D.
Dodging the Tubercle Bacillus in a Tuberculosis Hospital—Ezra Bridge, M.D.
Irregular Discharges as a Medical-Social-Administrative Problem in Tuberculosis—D. E. Quinn, M.D.
Are They Irregular Discharges or Irregular People?—D. E. Quinn, M.D.

These articles were written by associates of the Committee. They were obtained through the efforts of Committee members. Credit for securing them is given after the name of each author:

- Medical Social Worker in a Tuberculosis Control Program*—Clara Sanford (Secured by Maurice Campagna, M.D.)
The Tuberculosis Sanatorium and Its Relationship to Public Health Agencies—Glen W. Doolen, M.D. (Secured by Harry D. Clark, M.D.)
TB Tests in Schools—Pro and Con—Alton S. Pope, M.D. (Secured by the Chairman)
Rehabilitation of the Tuberculous Employee—C. Roger Allison, M.D. (Secured by the Chairman)
Why They Leave against Advice—I. D. Bobrowitz, M.D. (Secured by the Chairman)
County Sanatorium Explores New Field—S. Eric Simpson, M.D. (Secured by the Chairman)
Tuberculosis Control in Hawaii—Robert H. Marks, M.D. (Secured by the Chairman)
Relationship between Tuberculosis Association and the Local Medical Society—Carl R. Howson, M.D. (Secured by the Chairman)

Not all of the articles have been printed in the BULLETIN at this date, but they will continue to appear from month to month until the supply is exhausted.

The opportunity to write on medical subjects for a lay audience is a challenge to one's ability to express in ordinary English the obtuse, scientific thoughts that surround most medical men. It requires clear thinking and an ability to handle the English language. Among the medical profession too little of this type of writing is done.

The Committee recommends the work be continued and that another group of Trudeau members be appointed as members.

Report of the Committee on Medical Program

- Dr. John H. Skavlem, *Chairman*
 Dr. Emil Bogen
 Dr. Donald S. King
 Dr. Max Pinner (*ex officio*)
 Dr. Herbert C. Maier
 Dr. Sidney J. Shipman

The first meeting of this Committee was held in New York on September 12, 1946. At this time the general scheme and plan of the program was determined.

Each member of the Committee was assigned the responsibility of arranging for one of the scientific sessions.

The second meeting of the Committee was held in New York on February 7, 1947. At this time the reports of each section were brought together and the tentative program outlined. Since then the final details have been handled by correspondence, wire, and telephone.

The scientific sessions are as follows:

Wednesday, June 18, 1947, 9:50 a.m.

Emil Bogen, M.D., Olive View, California, *Chairman*.

Symposium on Use of Streptomycin and Other Anti-bacterial Agents in the Treatment of Tuberculosis.

Wednesday, June 18, 1947, 2:00 p.m.

Herbert C. Maier, M.D., New York, New York, *Chairman*.

Session on Surgery.

Thursday, June 19, 1947, 9:50 a.m.

Sidney J. Shipman, M.D., San Francisco, California, *Chairman*.

Symposium—Nontuberculous Pulmonary Diseases.

Thursday, June 19, 1947, 2:00 p.m.

Herbert L. Mantz, M.D., Kansas City, Missouri, *Chairman*.

Symposium—Pulmonary Diseases in Industry.

Thursday, June 19, 1947, 8:00 p.m.

Clinico-Pathological Conference.

Harold G. Trimble, M.D., Oakland, California, *Chairman*.

Panel: Herbert C. Maier, M.D., New York, New York;

Julius L. Wilson, M.D., New Orleans, Louisiana;

Carl C. Birkelo, M.D., Detroit, Michigan;

Wm. H. Hatfield, M.D., Vancouver, Canada.

Friday, June 20, 1947, 9:50 a.m.

Medical and Public Health Sections—Joint Session.

Tuberculosis as a World Problem.

Speakers: Johannes Holm, M.D., Copenhagen, Denmark;

Hector Orrego Puelma, M.D., Santiago, Chile.

An innovation at this program will be three seminars. At first it was planned to make these breakfast sessions. Technical difficulties, involving expenses, hotel management, and labor unions, made such plans seem prohibitive. There will be no breakfasts. These seminars are to be called at 8:15 a.m.

The following seminars have been arranged:

Wednesday, June 18, 1947, 8:15 to 9:15 a.m.

Harold M. Coon, M.D., Madison, Wisconsin, *Moderator*.

Management of Pulmonary Tuberculosis in General Hospitals.

Thursday, June 19, 1947, 8:15 to 9:15 a.m.

Henry C. Sweany, M.D., Chicago, Illinois, *Moderator*.

BCG.

Friday, June 20, 1947 to 9:15 a.m.

Howard W. Bosworth, M.D., Los Angeles, California, *Chairman*.

Significance and Care of Early Lesions of Pulmonary Tuberculosis.

AMERICAN TRUDEAU SOCIETY

Report of the Committee to Advise with the Editor of The American Review of Tuberculosis

Dr. Ezra Bridge, *Chairman*
 Dr. John H. Skavlem
 Dr. James J. Waring
 Dr. Julius L. Wilson

The functions of this Committee were stated in a letter dated February 25, 1947 from Dr. H. McLeod Riggins, President of the American Trudeau Society. These functions were listed as follows: "to confer with the Editor of the REVIEW in regard to two distinct matters; (1) on nominations of the Editorial Board of the REVIEW and (2) on articles for the REVIEW."

The major energy of the Committee was devoted to the development of a plan to circularize the members of the American Trudeau Society for their suggestions regarding the type and character of articles they would like to see in the REVIEW. On May 1, 1947, word was received from the Editor of the REVIEW, stating that at a meeting of the Editorial Board this procedure was not recommended. Immediately the plan was cancelled.

Steps were taken to secure specific articles for the REVIEW from men qualified in different fields. Twenty-five titles were suggested by the Editor. These were sent to members of the Committee and suggestions for authors made. No articles have been obtained. This lack of progress was the result of giving major attention to the circularization plan.

Suggestions were received from the Editor and from the Committee that critical reviews on some phase of chest diseases be included in each issue. This seems an excellent idea, but at the present time has not culminated in finding anyone to write the reviews.

The meeting of the Council of the American Trudeau Society, June 9, 1946, in Buffalo, recommended that three members of the Editorial Board be changed according to seniority. Due to change in September are Dr. Esmond R. Long, a member since 1930; Dr. Frank S. Dolley, since 1938; and Dr. Bruce H. Douglas, since 1938. Men to fill these places have not yet been selected, but they can be found before September of this year. Correspondence on these selections is under way.

Recommendation of the Committee is that it be continued but that new personnel be appointed.

Report of the Committee on Pan-American Relations

Dr. Henry C. Sweany, *Chairman*
 Dr. John Alexander
 Dr. Jose I. Baldo
 Dr. Kendall Emerson
 Dr. Fernando D. Gomez
 Dr. Esmond R. Long
 Dr. Gilberto S. Pesquera
 Dr. Max Pinner
 Dr. Hector Orrego Puelma

The Committee has had no meetings during the year but several problems have been discussed by correspondence.

It is gratifying to know that the idea of corresponding memberships has been approved by a number of Latin-American physicians and forty have availed themselves of this privilege and appropriate certificates have been sent each member.

The Spanish NEWS LETTER prepared by Dr. G. S. Pesquera has probably been the best single step taken to inform our friends to the south of events in this country. While most Latin-American tuberculosis physicians can read English they appreciate being met on equal terms and have their language recognized.

The problem of a reduction in residencies and fellowships for Latin-American students and physicians in this country has become acute and many of them feel it keenly. Your Committee, when in Lima recently, took pains to explain the reasons for much of the lag. It will probably be well to repeat it here for emphasis and for those whom we could not reach at Lima. There are two principal reasons: First, since so many of our own young doctors were away for three to five years during the war, we were obliged to give them first call on residencies on their return. This fact alone has filled practically all vacancies for perhaps as many years as the war lasted. A second cause is the deplorable state of most other countries of the world to whom we must allot some post-graduate positions to help in the whole tuberculosis problem which respects no boundaries.

We shall make an inventory of our vacancies, however, and give to our good neighbors to the south all places possible.

It may be worthy of recording here that, through the efforts of your Chairman, the Board of Directors of the Municipal Tuberculosis Sanitarium set up at their institution two residencies, each, a year in pathology for the Latin-American and Anglo-American physicians, respectively. The residencies are to run concurrently and include board, room and laundry.

Your Committee also begs to report on the recent meeting of the ULAST at Lima, Peru, March 17 to 23, 1947. Three delegates represented the National Tuberculosis Association and American Trudeau Society. They were:

Howard W. Bosworth, M.D.

Gilberto S. Pesquera, M.D.

Henry C. Sweany, M.D.

The program included three topics, namely, *Mass Surveys*, *Tuberculous Tracheobronchitis*, and *Economic and Social Assistance*.

As is the custom for these meetings, there are special committees appointed to "evaluate" and "summarize" the various topics discussed.

Concerning the first subject, *Mass Surveys*, it was agreed:

1: To intensify the program of mass examinations with systematic periodic tuberculin and photofluoroscopic surveys, beginning with groups of suspected maximum prevalence and taking the rest when economically feasible.

2: To establish surveys among government employees, social insurance beneficiaries, in health centres and dispensaries, in hospital admission wards and clinics and by means of mobile units to reach suburban and rural communities.

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- 3: To establish the necessary laboratory facilities in connection with the surveys in order to properly diagnose etiology and activity in cases with X-ray findings.
- 4: To seek adequate legislation and other provisions for the economic protection of newly found cases.

Regarding the second subject, *Tuberculous Tracheobronchitis*, it was concluded:

- 1: That the term Tuberculous Tracheobronchitis should include the lesions of the lesser bronchi, located outside of the field of endoscopic visibility as well as those of the major bronchi and trachea.
- 2: That routine bronchoscopy be carried out in all cases with clinical or X-ray signs pointing to bronchial involvement, but systematic bronchoscopy should be reserved only for institutions with special endoscopic departments. The organization of such departments in all large tuberculosis centres is highly recommended.
- 3: That bronchial lesions should not be regarded as a contraindication *per se* to pulmonary collapse or resection. Each case should be given special consideration, with treatment of the pulmonary lesion as the main objective.
- 4: New methods of local and general treatment should be constantly tried in view of the unreliability of present therapeutic measures.

On the matter of *Economic and Social Assistance* to the tuberculous and their dependents, it was advised:

- 1: To promote wide-scope social security systems in the Latin-American countries, as these enact special measures for the protection of the tuberculous.
- 2: That until such time as these social security systems be implemented, it is urgent to adopt emergency measures in favor of the tuberculous patient and his family.
- 3: That Latin-American governments be urged to reconsider and reform existing social and labor legislation in order to include special provisions in favor of those afflicted with tuberculosis.

It was further arranged that the next, or VIII Pan-American Congress of Tuberculosis be held at Mexico City early in 1949 and presided over by the distinguished Mexican phthisiologist, Dr. Ismael Cosio Villegas with Dr. Fernando Gomez of Montevideo still remaining Secretary General.

The following are the subjects to be considered at the 1949 meeting:

- 1: Tuberculosis in its relation to labor.
- 2: An appraisal of surgical treatment.
- 3: Cardio-respiratory factors in tuberculosis.

The Committee wishes to urge that all of us who can, should attend this important Congress. We feel sure that the President-Elect, Dr. Cosio Villegas, and his colleagues will do their utmost to make the Congress a success and will extend all of us a hearty welcome.

Report of the Committee on Rehabilitation

Dr. Norvin C. Kiefer, *Chairman*

Dr. Donald Covalt

Dr. Thomas N. Sheen

Dr. N. Stanley Lincoln

Dr. Rollin D. Thompson

Dr. Ernest S. Mariette

Mr. Holland Hudson (NTA)

Mr. Clarence W. Kehoe (NCTS)

The meeting of the Committee on Rehabilitation of the American Trudeau Society was held in New York City on January 17 and 18, 1947. Committee members in attendance were: Dr. Norvin C. Kiefer, Chairman; Dr. Donald Covalt; Dr. N. Stanley Lincoln; Dr. Thomas N. Sheen; Mr. Holland Hudson; Mr. Clarence W. Kehoe; and *ex officio*, Dr. Cameron Guild.

The Committee considered two definitions in rehabilitation which were adopted by the Conference on Rehabilitation of the Tuberculous in Washington, D. C., March, 1946. The Committee moved to adopt these definitions and recommended that the American Trudeau Society endorse them:

"Rehabilitation in tuberculosis is the restoration of tuberculous persons to the fullest physical, mental, social, vocational and economic usefulness of which they are capable."

"Vocational rehabilitation in tuberculosis means any services necessary to render a tuberculous person fit to engage in an occupation suitable to health and aptitude."

The question of the administration of in-sanatorium rehabilitation programs was discussed at considerable length. It was agreed that the direction of the rehabilitation program in the sanatorium is a responsibility of the institution. It was further agreed that a staff physician should head such a program. The chief reasons for this opinion were that the staff physician is in the most favorable position to direct any program which must be under constant medical supervision; that the physician would not be so directly concerned with inter-departmental affairs and frictions as other members of the professional team might possibly be; and that the idea of having a physician assigned to head the program would, in general, be readily acceptable to the various members of the rehabilitation team. It was noted that the most difficult problem would be that of interesting the physician in the program. The Committee, therefore, adopted the following resolution:

"The direction of the professional aspects of the rehabilitation program should be in charge of a physician. This responsibility may either be assumed by the Medical Director himself or may be delegated by him to a physician on his staff. The physician in charge of the rehabilitation program may in turn delegate some of the actual administrative work to the other members of the rehabilitation staff."

The Committee approved of the action of the Conference on Rehabilitation of the Tuberculous in Washington, D. C. where the term "rehabilitation counselor" was adopted as the best descriptive title for that person who has been

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variously designated as "rehabilitation counselor," "vocational counselor," "rehabilitation specialist," etc. The Committee approved a recommendation that the term "rehabilitation counselor" be accepted for general use.

In line with the policy adopted in January, 1947 by the Advisory Committee on Rehabilitation of the National Conference of Tuberculosis Secretaries, the Committee passed the following resolution:

"In order to maintain a high professional standard in rehabilitation work and to give the applicant for the National Tuberculosis Association's orientation course in rehabilitation an opportunity to get the most from orientation, the Committee recommends that preference be given to individuals whose academic background, special training, personality etc., are such as to fit advantageously into hospital assignments."

The Committee further approved the action of the Rehabilitation Service of the National Tuberculosis Association to establish standards or qualifications for rehabilitation counselors, including those who are selected for training as counselors. It was recommended by the Committee that the Rehabilitation Service be encouraged to develop standards, in consultation with interested official and voluntary agencies.

The results of the questionnaire on extra-medical management, which had been sent to sanatorium directors by the Committee, were discussed and it was decided to release a general summary of the findings.

The Committee discussed the problem of patients who leave the sanatorium against medical advice and the relation of statistics to be used to compare program. It was noted that the collection of statistics to be used to compare results in various hospitals is difficult because of the lack of uniformity of application of various terms relating to such discharges. The Committee, therefore, made the following recommendation to the Council of the American Trudeau Society:

"That a committee be established to study the problem of classification of hospital discharges and to formulate standards therefor so that experience can be comparable."

The need for a specific definition of the following terms was stressed:

- (a) Maximum hospital benefit.
- (b) Discharge against advice but with consent.
- (c) AWOL.
- (d) Temporary discharge for compelling personal reasons.
- (e) Against medical advice.

Methods for more extensive education of physicians in the procedures used in rehabilitation were considered. It was learned that the Veterans Administration is planning to initiate two- to six-week courses in rehabilitation of the tuberculous for their physicians. It was therefore hoped that a certain amount of information on rehabilitation could be introduced in the courses on post-graduate medical education which are being sponsored by the American Trudeau Society.

The need for more exact information concerning certain aspects of the rehabilitation projects was discussed. As a result the Committee approved the following motion:

"The Committee feels that the absence of sufficient data on the physical aspects of rehabilitation and on functional tests and the lack of adequate job analysis in relation to physical demands would warrant specific studies. There is also a need for adequate statistical follow-up studies in rehabilitation. The Committee recommends that the need for such studies be brought to the attention of the Rehabilitation Service of the National Tuberculosis Association, the Office of Vocational Rehabilitation, the Tuberculosis Control Division of the U. S. Public Health Service and other interested agencies."

The need for new classifications, which would be useful to all workers interested in rehabilitation of the tuberculous, was discussed at considerable length. Among these needs were the following:

- (a) Alignment of the rehabilitation classification with the general diagnostic classification to be recommended by the National Tuberculosis Association.
- (b) An improved prognostic classification.
- (c) A new type of activity prescription.
- (d) A comprehensive functional classification based upon work tolerance.

An outline of these classifications, based on one proposed at the Washington Conference on Rehabilitation of the Tuberculous, was considered and given temporary approval. The Committee proposed that this outline be given every consideration in the revision of Diagnostic Standards. A detailed description of these proposed classifications was therefore sent to Dr. John D. Steele. After a consideration of the coördination of the in-sanatorium and the post-sanatorium programs, the Committee emphasized, on motion, the need for:

- "1. Continuity of the rehabilitation program on the part of all professional groups interested, from the in-sanatorium to the post-sanatorium phases.
- "2. Coördination of the efforts of all of these professional groups in the post-sanatorium phase with free interchange of information."

Finally, in consideration of the question of the selection of candidates for rehabilitation among patients, the following resolution was adopted:

"The Committee feels that the exclusion of groups from rehabilitation projects because of age, education, sex, color, or occupation is against the principles of rehabilitation. The Committee believes that those who might be excluded because of these factors are the very ones who most need rehabilitation service and who would be most benefited by a sound rehabilitation program."

Report of the Committee on Tuberculosis in Industry

Dr. James M. Carlisle
Dr. Eugene J. Gillespie
Dr. Anthony J. Lanza
Dr. Raymond C. McKay

Dr. Lloyd Hamlin, *Chairman*
Dr. Oscar A. Sander
Dr. William A. Sawyer
Mr. B. E. Kuechle (NTA)
Wm. Arkwright Doppler, Ph.D. (NCTS)

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The Committee on Tuberculosis in Industry met in Chicago, Illinois, on February 15, 1947. At this meeting it was suggested that a member of the National Conference of Tuberculosis Secretaries be appointed to serve on the Committee. Mr. Glenn Armstrong, president of the National Conference of Tuberculosis Secretaries, in March, 1947, appointed Mr. Doppler to serve for the balance of the year.

The Committee adopted the following resolution on the death of Dr. Leroy U. Gardner:

RESOLVED, That the Committee on Tuberculosis in Industry wishes to express its sorrow and deep feeling of personal loss caused by the death of Dr. Leroy U. Gardner. His leadership, especially in the field of industrial medicine, has been a shining example of ethical standards and will be an inspiration in the work that lies ahead. His inherent modesty and sincerity endeared him to all who knew him. No problem was too big or too small to command his interest.

Specifically, Dr. Gardner's leadership and research in the field of silicosis made it possible for tens of thousands of workers to continue in their chosen fields. He made it apparent to industry that the disease was controllable. He gave us a new way of looking at tuberculosis and made possible the employment in industry of persons with inactive disease. He set higher standards by which to judge the value of the person. He had a profound understanding of the working man, especially in the dusty trades, but in his ardent labors for their happiness and well-being he did not lose sight of management problems.

The individual members of the committee have lost a friend; collectively, we have lost our mentor and most experienced counsel. The industrial world has lost a truly great physician. It is FURTHER RESOLVED, That a copy of this resolution be published in the next report of the Committee on Tuberculosis in Industry to appear in the AMERICAN REVIEW OF TUBERCULOSIS; and that a copy be incorporated in the minutes of the present meeting.

JOB PERFORMANCE OF TUBERCULOSIS PATIENTS IN INDUSTRY

This study is being conducted under the supervision of the National Tuberculosis Association Rehabilitation Service with the cooperation of the Committee on Tuberculosis in Industry.

The Committee feels that the problem of rehabilitation and employment of persons with inactive tuberculosis should be brought to the attention of management, personnel officers, general practitioners, and compensation administrators, all of whom need to be educated on this subject. Several suggestions were made for consideration by the Rehabilitation Service:

- (a) Publication of an article or pamphlet on job performance addressed to management and personnel officers.
- (b) Presentation of the findings at a meeting of the American Management Association or a similar group.

PUBLICATIONS

- a. *Industrial Job Placement of Persons with Inactive Tuberculosis—A Guide for Personnel and Employment Directors.* At the request of the Committee, Mr.

Richard Lutz of the Falk Corporation, Milwaukee, Wisconsin, prepared the draft of this pamphlet. Dr. Leroy U. Gardner, before his death, revised the manuscript. It was then edited by the Committee on Tuberculosis in Industry at its meeting in Chicago on February 15, 1947. The manuscript is now in the hands of the printer and will be ready for distribution early this summer. It will make a 12-page 6 × 9 pamphlet; 5,000 copies will be printed.

b. *Tuberculosis and Industrial Employment—A Code of Fair Employment Practices and Guide for Industrial Physicians.* This 16-page report of the Committee was published early in 1946. Three runs of 5,000 each were printed. The pamphlet needs revision but the Committee agreed to withhold another edition until the new *Diagnostic Standards* have been published.

c. *Industry and Tuberculosis—Viewpoints of Management and Labor.* This 20-page pamphlet produced in 1944 has been sold out for some time and it will not be reprinted. The Committee on Tuberculosis in Industry has suggested a similar publication containing articles by other authors. The selection of papers was left to Mr. Doppler, Secretary of the Committee. No progress can be reported at this time.

d. *Pamphlet for Compensation Administrators.* At its meeting in February, 1947, the Committee discussed the need for a pamphlet addressed to workmen's compensation administrators, describing good administrative practices with regard to making awards in tuberculosis claims where industrial factors are cited as proximate or aggravating causes.

Mr. B. E. Kuechle, Employers Mutual Liability Insurance Company, Wausau, Wisconsin, a member of the Committee, agreed to draft a manuscript for Committee discussion. The draft has not yet been received from Mr. Kuechle.

e. *Atlas of Industrial Chest Plates.* The publication of an atlas on chest plates was suggested by the Committee. It has been delayed due to Dr. Gardner's death. There is a great need for this material and the Committee favors publication.

Dr. Arthur J. Vorwald (to be associated with Trudeau Sanatorium, July, 1947) has agreed to gather the material accumulated by Dr. Gardner. Publication will have to be held in abeyance until Dr. Vorwald has had an opportunity to submit the material to the National Tuberculosis Association.

Report of the Committee on Revision of Diagnostic Standards

Dr. Ralph Horton, *Chairman*

Dr. Howard W. Bosworth
Dr. W. Edward Chamberlain
Dr. Ismael Cosio Villegas
Dr. Herman E. Hilleboe
Dr. Edgar Medlar

Dr. Hector Orrego Puelma
Dr. Oscar A. Sander
Dr. John D. Steele
Dr. George J. Wherrett
Dr. Roy A. Wolford

The work of the Committee has continued during the year by correspondence and one meeting was held in New York City on November 29, 1946. Preliminary

revisions of various chapters of the *Standards*, which have been prepared by individual Committee members and subcommittees, are now in hand for about three-fourths of the material contained in the 1940 edition of *Diagnostic Standards*. The chapter on "Laboratory Procedures" is being rewritten by the American Trudeau Society Committee on Evaluation of Laboratory Procedures. The section on "Rehabilitation" was written in collaboration with the American Trudeau Society Committee for that activity, and the section on "Case-finding and Mass X-ray Surveys" was written in collaboration with the Committee on Tuberculosis in Industry. Other committees have made many constructive suggestions.

The remaining work to be done in the completion of a tentative revision of the *Standards* will be completed within a few months and ready for limited trial during the autumn months. It is hoped that a final report can be made at the annual meeting in 1948.

Report of the Committee on Evaluation of Laboratory Procedures

Dr. C. Eugene Woodruff, <i>Chairman</i>
Dr. Emil Bogen
Dr. Edwin A. Doane
Dr. M. L. Furcolow
Dr. Max Lurie
Dr. Edgar Medlar
Mr. William Steenken (NTA)

During the past year the Committee on Evaluation of Laboratory Procedures has had two special problems: first, the revision of the laboratory section in *Diagnostic Standards*. The preliminary revision has now been written. Second, we have attempted to evaluate various media proposed for the primary isolation of tubercle bacilli. This is a long-term study and is still in progress. At a brief meeting of our Committee, held in Buffalo a year ago, it became evident that additional help would be needed in the study of culture media. Accordingly, the Committee on Medical Research of the National Tuberculosis Association was approached with the request that a special study of culture media be subsidized. This request was generously granted and the special study has been in progress since last October at the Trudeau Laboratory, under the direction of Mr. William Steenken, Jr., and at the Laboratory of the Barlow Sanatorium Association, under the direction of Dr. C. Richard Smith. Also the study has been furthered through the voluntary coöperation of a unit of the National Institute of Health at Bethesda, under the direction of Dr. M. I. Smith, and the coöperation of all the members of the Committee on Evaluation of Laboratory Procedures who had laboratory facilities available.

The qualities particularly sought after in the culture medium were: the ability to initiate growth of tubercle bacilli quickly and surely; the ability to suppress the growth of contaminating microorganisms; and, finally, the ability, in positive cultures, to produce typical colonies of tubercle bacilli. After eight months study the majority of the Committee is on the opinion that a medium with egg-yolk, potato, glycerine and water as basic ingredients remains the most

practical for general laboratory use. Data on this problem are still being gathered.

With regard to culture media we should like to emphasize the need for some method of rapidly and surely confirming the diagnosis of tuberculosis. This need is pointed up not only by the large number of X-ray surveys presently in progress across the nation, but it is pointed up also by the rapid extension in the use of streptomycin and the need for establishing, first, whether or not a given case is actually tuberculosis and, second, whether or not any marked changes occur in the bacillary content of the sputum following therapy.

In following up this need your Committee has been keenly interested in the various formulae for liquid media which have been proposed recently; many of these formulae have been tried. However, the liquid media thus far available have been beset with two major difficulties; first, with regard to the growth of contaminants and, second, with regard to the ready identification of tubercle bacilli if they should be present in the culture. Because of these difficulties the Committee has gone on record with the opinion that, at the present time, liquid media cannot be recommended for use in routine diagnostic procedures. On the other hand, the possibility is recognized that liquid media may have a special function in the culturing of body fluids such as blood or spinal fluids which are usually not contaminated with pyogenic bacteria.

As already implied, the laboratory, during the past year, has felt the impact of streptomycin therapy just as the clinicians have. Its wide-spread use has introduced many new laboratory problems. At the moment these problems are in the hands of a special Streptomycin Laboratory Committee. However, as the new techniques become standardized, they too will have to be evaluated and incorporated in the procedures of every well ordered laboratory interested in tuberculosis work.

Report of the Committee on Sanatorium Planning and Construction

Dr. Hugh B. Campbell, *Chairman*

Dr. Ralph Horton

Dr. Rollin D. Thompson

Dr. Myron D. Miller

Dr. Henry Ware Walters

Dr. Robert E. Plunkett

Dr. Robert L. Yeager

Dr. H. McLeod Riggins

Mr. J. B. Basil, R.A. (NTA)

Miss Suzanne H. Harrison, R.N. (NTA)

The publication in the late fall of 1946 of the manual *Tuberculosis Hospital Planning and Construction* completed the work of the Committee on Sanatorium Planning and Construction, appointed approximately three years ago.

In 1945, the earlier publication of this Committee was made available to any who might be interested in tuberculosis hospital construction. It contained plot and floor plans for a hospital building capable of housing 200 patients.

These two publications supplement each other and should provide, for a number of years to come, most of the essential facts and ideas necessary for sanatorium planning and construction.

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Report of the Committee on Tuberculosis in General Hospitals

Dr. Leopold Brahdy, *Chairman*
 Dr. Theodore L. Badger
 Dr. Robin C. Buerki (AHA)
 Dr. William H. Oatway, Jr.

The Committee is a joint project of the American Hospital Association, the United States Public Health Service, and the American Trudeau Society.

In the fall of 1946 the three societies coöperated in the production and distribution of "kits" on chest X-rays for all hospital admissions. Each "kit" consisted of a series of leaflets on various aspects of the subject, all intended to aid hospitals to plan case-finding among their admissions. It was a useful venture and has aroused much interest.

As was to be expected, problems have arisen. In some localities, in spite of approval by health authorities, hospital administrators feel this is a public health activity and not their function. In other localities we hear of a reverse reaction: public health officers looking askance at work which overlaps their own field. In all places, questions arise on how the clinician, the radiologist, the hospital administrator, and public health officer can best work together. No doubt the solution of the problems must vary from place to place.

Developments in tuberculosis control and modern community-hospital relationships require that general hospitals join in a tuberculosis program. In this field, specialists, public health officers, and roentgenologists can contribute to the sound administration of general hospitals. Although the number of hospitals doing tuberculosis control work is increasing, the number is still quite small and the work is not well integrated with community health work. The share of the hospital in the control of tuberculosis in the community is inseparable from the control of occupational tuberculosis among its own personnel and the protection of the hospital patients.

With the addition of two groups, the roentgenologists and the public health officers, a future joint committee could be formed which would represent all those whose work is essential for efficient control of tuberculosis within general hospitals. The 1946-1947 Committee's main task was to obtain the coöperation of these two groups.

This has now been accomplished: The American Public Health Association has nominated as representative on a future committee, Dr. Joseph C. Molnar, Deputy Commissioner of Health of Detroit, and Secretary of the Health Officers Section, American Public Health Association.

The American College of Radiology has nominated Professor W. Edward Chamberlain of Temple University.

The American Hospital Association has nominated Dr. Robin Buerki, University of Pennsylvania; Dr. John B. Barnwell, U.S. Veterans Administration; Dr. Ralph Snively, U.S.P.H.S.; and Dr. E. S. Mariette, Glen Lake Sanatorium, Minnesota.

The Committee recommends the appointment of a 1947-1948 joint committee

from these nominations, plus members from the American Trudeau Society. The U. S. Public Health Service expects to continue to be represented by a member of its staff, who will be designated for each meeting.

On January 15, 1947, a Committee meeting was devoted to exploring suggestions so that the proposed enlarged committee may have an agenda with which to start. The minutes are on file in the ATS.

In order to advance this coöperative effort, the Committee should be empowered to do educational work among the public, hospital administrators, public health officers, and roentgenologists. It should investigate and recommend practices and standards for the control of tuberculosis in hospital personnel, for case-finding among all admissions, and for all other procedures for tuberculosis control in which general hospitals should participate. It should take part in related projects undertaken by any of the five participating organizations. The letters of acceptance of the invitation to join the Committee from these two organizations are on file with the ATS.

Report of the Committee on Tuberculosis in Penal and Other Institutions

Dr. Robert E. Plunkett, *Chairman*
 Dr. Newton Bigelow
 Dr. Gustaf A. Hedberg
 Dr. Cedric Northrop
 Dr. Edward L. Ross

PREAMBLE

Definite information on the prevalence of tuberculosis in penal and correctional institutions throughout this country and Canada is almost entirely lacking. Neither morbidity nor mortality figures can be taken as a basis for an estimate, as the reporting of both cases and deaths depends on several factors which vary from one institution to another.

In New York State, for instance, there are 14 institutions administered by the Department of Correction. Two, not included in this statistical study, provide facilities for the isolation and treatment of tuberculous inmates. Of the other 12 institutions, only 3 reported cases from tuberculosis in 1939, and 6 in 1940. During the two-year period, 1939-1940, 25 cases were reported for a total population base of 29,724, which is equivalent to an annual reported case rate of 84.1 per 100,000, a rate slightly less than that estimated for the general population of Upstate New York. The average annual reported case rate in the 12 institutions for this two-year period varied from a minimum of 46.1 per 100,000 in one to a maximum of 325.1 in another. Reports of the Minnesota Department of Health indicate that from July 1, 1944 to July 1, 1946, only one tuberculosis death occurred among approximately 1,900 inmates of prisons and reformatories.

As yet, few extensive case-finding surveys have been made which would provide clues as to the extent of the tuberculosis problem. California has reported the results of case-finding surveys in 2 of its State prisons, using 35 mm. films. At Folsom Prison, in 1944, a total of 1,290 inmates were examined,

28 (2.2 per cent) of whom were found to have tuberculosis and 24 (1.8 per cent) were considered suspects. At San Quentin Prison, a total of 3,125 inmates were examined, 49 (1.6 per cent) of whom were found to have tuberculosis and 72 (2.4 per cent) were classified as suspects. The State of Washington has had a similar experience. Recently, in New York State, 1,917 inmates in one prison were examined with paper films and 6 (0.3 per cent) were found to have clinically significant tuberculosis.

However, the general impression seems to be that, while the tuberculosis problem in the penal institutions is not as great nor as acute as that of the mental hospitals, it is greater than that of the general population and therefore requires corrective measures for its reduction.

Generally speaking, a tuberculosis control program for the penal institutions may include the same procedures as those adopted for the mental hospitals, namely, (a) case-finding, (b) segregation of all active or probably active cases and (c) early discovery of cases which may develop subsequently.

However, in formulating such a program, careful consideration should be given to the fact that the penal institutions differ in many respects from all other custodial institutions. The various laws and regulations, and a lack of certain facilities and personnel may necessitate some modifications in the general plan. On the other hand, the administration of such a program should be more easily effected because the total population of the penal institutions is much smaller than that of the mental hospitals and the tuberculosis problem among the inmates is presumably not as great.

On the basis of a report compiled by the American Prison Association, in 1945, the capacity of prisons and penitentiaries, both State and National, was given as 121,181 with a total population of 93,321; the male population totaled 90,314 and the female 3,007. The State industrial schools and reformatories throughout the country had a total capacity of 54,814 with a total population of 44,048; the male population numbered 34,554 and the female 9,494. In other words, the group with which a tuberculosis control program would be concerned would total approximately 150,000 individuals, including employees.

SUGGESTED CONTROL PROGRAM

(1) An initial case-finding survey among both inmates and employees will provide data for an appraisal of the prevalence of tuberculosis in each institution. This first survey could be carried out either by first tuberculin testing all inmates and employees and then X-raying only the positive reactors, or by X-raying the entire population of the institution. The second method would seem to be the more practical and in the end also more economical, particularly if photographic equipment is available. Inasmuch as many of the institutions lack proper X-ray equipment and in some cases do not even have a full-time medical staff, it is recommended that these surveys be integrated with the activities of the tuberculosis division of the State Health Department, so that standards of procedure and of diagnosis may be developed on a state-wide basis. In those states where special provisions have already been made for the

establishment of a tuberculosis control program in mental hospitals, it would be advantageous from the practical as well as from the economical point of view to expand such a program to include the penal institutions.

It is to be noted that these recommendations would apply only to penal institutions which are under direct State administration, and perhaps at a later time to county and city jails, utilizing available health services. It does not seem likely that they could apply to Federal prisons over which the State has no jurisdiction. The U. S. Public Health Service is entrusted with this responsibility and may delegate it to local authorities.

(2) All cases of reinfection tuberculosis found among the employees should be referred to the nearest tuberculosis hospital or clinic for further study and follow-up. Those who are found to have active tuberculosis should be relieved from duty and receive proper treatment. Those who have inactive tuberculosis should remain under the supervision of the clinic staff and be reexamined whenever indicated.

(3) All inmates found to have tuberculosis should be studied, particularly by sputum examinations, in order to determine the clinical status of their disease. All reportable cases should be reported to the Public Health authorities. All those who have clinically significant tuberculosis, that is, active or potentially active disease, should be segregated and receive treatment. Major difficulties may be encountered in this phase of the program because very few prisons and penitentiaries have facilities for the proper segregation and care of tuberculosis cases over protracted periods. Even where special facilities are available for the segregation of tuberculous criminals, the laws and the penal system of the State may prevent their commitment to these institutions; until recently in New York State, only certain types of criminals could be transferred to the tuberculosis wards of the 2 prisons designated for segregation and treatment of infectious cases.

In view of the fact that the number of cases of tuberculosis to be found in the prisons of most states would be too small to warrant the establishment of segregation facilities in every prison, it should be recommended that such facilities be made available in at least one prison in every State, and that the penal laws be modified wherever necessary to permit the transfer of all tuberculous criminals to that prison.

Similar problems are presented by the industrial schools and reformatories. However, considering the younger age of the inmates in these institutions, it is to be expected that the tuberculosis problem presented by them would be relatively small. In a survey made a few years ago at the New York State Vocational Institution in Coxsack, no cases of tuberculosis were found among the 639 inmates examined. In view of the fact that most of the boys and girls in the reformatories are behavior and not criminal cases, it should be recommended that the disposition of the relatively few tuberculous cases among them be decided for each individual. As the result of a consultation between the Correction Department and Health authorities, tuberculous inmates of the criminal type and with long sentences would undoubtedly be transferred to a prison which

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has segregation facilities, while all other cases could be paroled and transferred to State, county or city tuberculosis hospitals.

(4) Once the initial case-finding survey of a prison has been completed, continuous diagnostic service should be established. Such a service would include (1) chest X-rays of all new employees, (2) examinations of recently admitted inmates and (3) resurveys at stated periods of that portion of the institutional population (inmates and employees) examined in the first survey. All new employees should receive preemployment X-ray examinations of the chest; those who are found to have reinfection tuberculosis should be referred to the nearest tuberculosis clinic or hospital for determination of their clinical status before they are given permanent employment.

As for the recently admitted inmates, the screening could be done by one of two methods: (1) X-ray all new inmates soon after commitment, and segregate those who show evidence of clinically significant tuberculosis; (2) tuberculin test all new inmates, X-ray the positive reactors and segregate the ones showing clinically significant tuberculosis. This second method may be more practical and economical, particularly in the industrial schools and reformatories. Also, if this method is chosen, consideration should be given to the advisability of vaccinating with BCG all negative reactors.

All X-ray films taken in the course of these screenings should preferably be referred for interpretation to the same agency which has had the responsibility for the initial survey. However, local conditions may not permit the adoption of such routine. The institutions may lack the X-ray equipment and personnel; on the other hand, the central agency may not be in a position to supply the continuous service. Under such circumstances, it may be more practical to make arrangements with the tuberculosis clinic or hospital nearest to the penal institution. Its personnel could then assume the responsibility not only for these activities, but also for any consultation service which the penal institution may require.

On the basis of past experience, it is to be expected that a certain number of new cases of tuberculosis will continue to develop among the inmates after the initial screening and segregation of the infectious cases. Therefore, periodic resurveys will be necessary, the first one to be made preferably one year after the first survey. The frequency of resurveys thereafter should be determined mainly by the findings of the first two surveys. In general it may be possible to schedule such resurveys at two-year intervals.

(5) The selection and establishment of segregation facilities for the tuberculous inmates should be made in consultation with the Department of Correction and Public Health authorities so that prophylactic measures and medical and nursing services can be applied with the preservation of the necessary penal regulations and with standards commensurate with modern tuberculosis medical practices. All prophylactic measures practiced in a modern tuberculosis hospital should be applied for the protection of the personnel assigned to the care of tuberculous inmates. Inmates who are eligible for parole should receive chest X-rays. Evidence of tuberculosis in any of these parolees should be

reported to the parole board. Parole should then be deferred until arrangements are made for appropriate care of the individual in the community to which he is to be paroled. All tuberculous parolees should be reported to the public health authorities at the time of their parole so that they can be kept under medical supervision upon their return to the community. It is recommended that arrangements be made whereby local health authorities shall be notified in advance of the discharge of any tuberculous inmate from jails, penitentiaries or prisons.

Report of the Committee on Undergraduate Medical Education

Dr. Robert G. Bloch, *Chairman*

Dr. Arthur C. Bachmeyer

Dr. Victor Johnson

Dr. Loren Chandler

Dr. Donald S. King

Dr. Harold M. Coon

Dr. John MacMillan

The discussions of the Committee on Undergraduate Medical Education at its meeting on February 12, 1947 followed the lines established in the Committee's report for 1946 (*Am. Rev. Tuberc.*, October–November, 1946, 54, 456). In that report the following recommendations were advanced as the most important for an improved teaching program for undergraduate medical students:

- 1: The training in tuberculosis in combination with education in other pulmonary diseases.
- 2: The integration of such education with instruction in all other phases of medicine and surgery and consequently the centralization of the essential training in teaching centres with general hospital facilities.
- 3: The procurement of instructors competent in the teaching of general internal medicine as well as of pulmonary diseases.

In this year's discussions the Committee elaborated on these requirements and represents its views to the Council with more detailed recommendations.

Because of the hesitancy which became manifest in some quarters in accepting the transfer of essential teaching from sanatoria to general hospitals, the Committee emphasizes that it recognizes the value of the sanatorium for the treatment of tuberculosis as well as for teaching in the field of tuberculosis. However, the Committee wishes to reiterate its recommendation of last year regarding the importance of centralizing education in pulmonary diseases in general hospitals with facilities for the diagnosis and treatment of tuberculosis. In this connection, it is the considered opinion of the Committee that, when the construction of new facilities for the care of the tuberculous becomes necessary, these facilities should be placed in connection with or in close proximity to general hospitals for teaching purposes.

Toward the same goal the Committee repeats last year's recommendation requesting fellowship funds for the training of teachers in internal medicine with special emphasis on thoracic diseases. Further, on motion, the Committee recommended to the Council of the American Trudeau Society that the various foundations and agencies interested in tuberculosis, the state and local associa-

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tions and health departments and medical societies be approached for funds to provide for the training of teachers in the field of pulmonary diseases.

To be eligible for such fellowship assistance the recipient should have an aptitude for teaching, should be eligible for or seeking certification by the American Board of Internal Medicine and should have additional training in the Specialty of Chest Diseases, which may include sanatorium experience and work in a recognized teaching centre devoted to chest diseases. This assistance is to be for a yearly period which may be extended if indicated. Since the procurement of specially trained instructors for undergraduate students thus extends into the field of graduate education, the Committee discussed its propriety for making recommendations for teacher training. It was the consensus that under the circumstances it was within the province of the Committee to work on recommendations for such a program.

Because of the great importance of X-ray diagnosis in the teaching of pulmonary diseases, the Committee reiterates its opinion that the indefinite preservation of X-ray records as teaching material is of great importance in a teaching hospital. In this regard the Committee also wishes to stress the need for chest X-ray examinations of all newly admitted patients in all hospitals in order to offer adequate protection against infection to students and hospital personnel as well as to provide adequate teaching material.

A booklet entitled *Surgery in Tuberculosis* had been submitted for the Committee's opinion as to the feasibility of its distribution to medical students together with *Diagnostic Standards* and *Chest X-ray Interpretation*. The Committee voted against the distribution of this booklet as a companion to the above mentioned two publications.

Report of the Committee on Postgraduate Medical Education National Committee*

Dr. John D. Steele, Secretary	Dr. Howard W. Bosworth, Chairman
Dr. Theodore L. Badger	Dr. Herman E. Hilleboe, Co-chairman
Dr. John B. Barnwell	Dr. Max Pinner
Dr. Kendall Emerson	Dr. Harold G. Trimble
Dr. Esmond R. Long	Dr. James J. Waring
Dr. Paul P. McCain ²	Dr. George J. Wherrett
	Dr. Julius L. Wilson
	Mr. C. W. Kammeier, Representative NCTS

The plan for this project was developed by Dr. H. McLeod Riggins, President of the American Trudeau Society. A Committee was appointed so that the Society's program of postgraduate medical education could parallel the efforts now being put forth in the field of health education. It appeared that postgraduate medical education was lagging far behind this work in other fields.

* For membership of Regional Committees see end of Report.
² Deceased.

Seven Regional Committees were set up throughout the United States and Canada, and a National Committee consisting of these chairmen and several advisors held its first meeting September 28, 1946, in Chicago. Objectives were outlined, policies determined, and the first pilot course planned. Two subcommittees, one on curriculum and faculty, and one on postgraduate medical education for the general practitioner, also were appointed at this time.

A one- or two-week intensive course limited to not more than 30 applicants was advised for each section as a joint project between the American Trudeau Society and the National Conference of Tuberculosis Secretaries with a portion of the expenses subsidized by the National Tuberculosis Association where necessary.

The pilot course was planned for the University of Wisconsin Medical School, March 3rd to 8th, with a meeting of the subcommittee on faculty and curriculum immediately following in New York on March 9th in order to disseminate the information acquired in the pilot course.

The following reports, by sections, present the work and plans to date:

Section I. Chairman, Dr. Theodore L. Badger, of Boston, reports that a fall course from November 10th to November 21st had been planned with the hope of participation of faculty members from Harvard, Tufts, Boston University, but, due to several problems which arose through the combination of these three medical schools, it was decided that the program should be given in the spring of 1948. Work is going on now to that effect.

Section II. Dr. Esmond Long, of Philadelphia, reports that tentative plans are underway for a course to be given in the late fall of this year or possibly spring of next year.

Section III. Due to the death of the Chairman, Dr. Paul McCain, in Sanatorium, North Carolina, the work of this Committee has been temporarily held up. Reorganization is now taking place and plans will be underway soon for the work in that area.

Section IV. Dr. Julius Wilson, of New Orleans, reports that plans are underway for a course there in the winter of 1947 and 1948.

Section V. Dr. John Steele, of Milwaukee, reports the success of a one week's pilot course held March 3 to 8, 1947. Of the 47 applications, 30 were accepted for matriculation. All data possible were compiled as a result of this course and used as a basis for study and recommendations for the subcommittee on faculty and curriculum. Tentative plans have been made for the next course to be held at Ann Arbor during the coming year.

Section VI. Dr. James Waring, of Denver, Colorado, reports a two weeks' course from July 28th to August 9th will be given at the University of Colorado School of Medicine. The programs are out and applications are now being received.

Section VII. Dr. Harold Trimble, of Oakland, California, reports that plans are underway for a course to be given by the University of California in cooperation with Stanford University Medical School during the week of December 1 to 6, inclusive, 1947.

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Section VIII. Dr. G. J. Wherrett, of Ottawa, Canada, reports that plans are underway for a postgraduate session in Montreal next winter, but the more distant parts of Canada will probably coöperate with the northern sections in the United States in the western areas, due to the distance and geographical problems involved in an all-Canada program.

The subcommittee on continuation study of chest diseases for the general practitioner under the chairmanship of Dr. Herman Hilleboe, of Washington, is recommending a two-point program as a pilot study for a national plan. The first is a short course at the Center for Continuation Study of the University of Minnesota. The second is an integration of the work through X-ray surveys with the program of the county medical societies. The aim is to bring the general practitioner directly into contact with survey work, interpretation of films, and the disposal of cases in his area and in his practice. If this is successful in Minnesota, it will be expanded to other states.

The subcommittee on curriculum and faculty compiled a very complete report with recommendations which were sent to all regional chairmen for distribution to their committee members.

CONCLUSIONS

Your Chairman wishes to thank all of the members of the National and Regional Committees for their coöperation in carrying out the objectives of this Committee. I also wish to thank the secretaries and the associations who are making much of this work possible, for, without their coöperation, much of it could not be carried out. I recommend the continuation of this Committee and the entire program as presented.

Region I

Theodore L. Badger, M.D. *Chairman*
 Kirby S. Howlett, Jr., M.D., *Co-Chairman*
 Hugh B. Campbell, M.D.
 John C. Ham, M.D.
 Donald S. King, M.D.
 Paul S. Phelps, M.D.
 Alton S. Pope, M.D.
 John W. Strieder, M.D.
 Mabel Baird, Representative NCTS

Region III

Paul P. McCain, M.D.,² *Chairman*
 Howard Bradshaw, M.D., *Co-Chairman*
 Thomas B. Aycock, M.D.
 Reese Berryhill, M.D.
 Rufus F. Payne, M.D.
 David T. Smith, M.D.
 W. Atmar Smith, M.D.
 Rollin D. Thompson, M.D.
 David H. Waterman, M.D.
 Frank W. Webster, Representative NCTS

² Deceased.

Region II

Esmond R. Long, M.D., *Chairman*
 Edward N. Packard, M.D., *Co-Chairman*
 J. Burns Amberson, M.D.
 David A. Cooper, M.D.
 Herbert R. Edwards, M.D.
 John Gibbon, M.D.
 C. Howard Marcy, M.D.
 G. Taggart Evans, Representative NCTS

Region IV

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 Henry Boswell, M.D.
 Maurice Campagna, M.D.
 H. Frank Carman, M.D.
 Lewis J. Moorman, M.D.
 Robert R. Shaw, M.D.
 Pansy Nichols, Representative NCTS

Region V

John D. Steele, M.D., *Chairman*
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 Robert G. Bloch, M.D.
 Harold M. Coon, M.D.
 Bruce H. Douglas, M.D.
 H. Corwin Hinshaw, M.D.
 Frank L. Jennings, M.D.
 Herbert L. Mantz, M.D.
 Henry C. Sweany, M.D.
 W. P. Shahan, Representative NCTS

Region VII

Harold G. Trimble, M.D., *Chairman*
 Sidney J. Shipman, M.D., *Co-chairman*
 Grover C. Bellinger, M.D.
 Emil Bogen, M.D.
 Carl R. Howson, M.D.
 John C. Jones, M.D.
 Cedric Northrop, M.D.
 W. F. Higby, Representative NCTS

Subcommittee on Faculty and Curriculum

John D. Steele, M.D., *Chairman*
 Theodore L. Badger, M.D.
 Esmond R. Long, M.D.

Subcommittee on Courses for the General Practitioner

Herman E. Hilleboe, M.D., *Chairman*
 Edwin J. Simons, M.D.
 Harold G. Trimble, M.D.

Region VI

James J. Waring, M.D., *Chairman*
 H. Dumont Clark, M.D., *Co-chairman*
 John F. Allen, M.D.
 F. R. Harper, M.D.
 Allan Hurst, M.D.
 Carl Mulky, M.D.
 Stuart Sanger, M.D.
 Helen L. Burke, Representative NCTS

Region VIII

George J. Wherrett, M.D., *Chairman*
 Hugh E. Burke, M.D., *Co-chairman*
 James D. Adamson, M.D.
 Robert G. Ferguson, M.D.
 William H. Hatfield, M.D.
 R. M. Janes, M.D.

**Report of the Committee on Therapy
 and its
 Subcommittee on Streptomycin**

Committee on Therapy

Dr. H. Corwin Hinshaw, *Chairman*
 Dr. John Adcock
 Dr. Kirby S. Howlett, Jr.
 Dr. John B. Barnwell
 Dr. Richard H. Meade, Jr. (*ex officio*)
 Dr. Robert G. Ferguson
 Dr. H. Stuart Willis (*ex officio*)

Subcommittee on Streptomycin

Dr. H. Corwin Hinshaw, *Chairman*
 Dr. Kirby S. Howlett, Jr.
 Dr. J. Burns Amberson
 Dr. Walsh McDermott
 Dr. Emil Bogen
 Dr. Carroll Palmer
 Dr. Paul A. Bunn
 Dr. Arthur M. Walker
 Dr. Robert P. Gearhart
 Dr. H. Stuart Willis

The Committee on Therapy of the American Trudeau Society and its Subcommittee on Streptomycin Therapy have, during the past year, carried out a

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series of therapeutic trials of streptomycin therapy in tuberculosis. In addition, the Committee has had the privilege of reviewing results of therapeutic trials conducted by the U. S. Veterans Administration, the U. S. Army and the U. S. Navy, and has reviewed results of work previously undertaken at Cornell University, Mineral Springs Sanatorium, and the Mayo Clinic. The American Trudeau Society has been closely affiliated with the work of the United States Public Health Section of the National Institute of Health of the United States Public Health Service. The Committee is collaborating closely with the Committee in Medical Research of the members of the Committee on Therapy and the Subcommittee on Streptomycin Therapy.³

(1) Intensive parenteral and intrathecal streptomycin therapy is advised for treatment of tuberculous meningitis. Although clinical remissions of varying duration are induced frequently by such treatment, subsequent relapse is likely to occur. Residual neurological disorders are frequently noted but complete clinical remission may be anticipated in a sufficient proportion of cases to justify treatment of all patients. Early diagnosis and prompt treatment appear to yield superior results, hence treatment must be instituted frequently before complete bacteriological data are available.

(2) Streptomycin therapy is advised for treatment of acute hematogenous miliary tuberculosis. Prompt treatment is necessary if best results are to be realized. Physicians are warned that nontuberculous pulmonary infiltrations may simulate miliary tuberculosis roentgenographically and wise clinical judgment is required to identify such lesions. Nevertheless if treatment of miliary tuberculosis is to be prompt, it may have to be instituted before bacteriological confirmation of diagnosis is available.

(3) Streptomycin therapy is advised for the treatment of more severe cases of tuberculous laryngitis and ulcerating tuberculous lesions of the mucous membranes of the oropharynx. The palliative clinical benefits of such treatment are sufficiently uniform and gratifying to justify trial of treatment even in some instances when the ultimate prognosis of associated pulmonary tuberculosis appears grave. Combined parenteral and topical treatment are suggested at this time, pending more complete information as to the relative merits of these two methods of administration.

(4) Streptomycin therapy is advised for treatment of progressive ulcerating tuberculous lesions of the tracheobronchial tree. Streptomycin should not be expected to benefit fibrous strictures of the tracheobronchial passages. Parenteral treatment should be employed in such cases. It is not clear as yet whether results are superior when combined aerosol and parenteral treatment is used.

(5) Streptomycin therapy is not indicated at this time for treatment of all types of pulmonary tuberculosis. Most suggestible results are noted following treatment of recent but extensive and progressing pulmonary lesions, especially

³ These statements are not to be construed as official statements of any of the U. S. Government agencies named above.

if these be diffuse and finely disseminated in appearance rather than appearing as large, dense and localized shadows in roentgenograms. However, tuberculous pneumonia should be treated with streptomycin. It is not recommended at this time that such lesions be treated unless the physician has reason to believe that conventional therapeutic methods will not suffice to control the disease.

Streptomycin cannot be recommended at this time for treatment of (a) chronic fibroid or fibrocaseous pulmonary tuberculosis, (b) acute destructive and apparently terminal types of pulmonary tuberculosis, (c) minimal or early moderately advanced pulmonary tuberculosis with favorable prognosis. These recommendations may be modified by subsequent experience, especially if the toxic effects of the drug enumerated below are found to be avoidable. It is important that tuberculosis with favorable prognosis be not treated with streptomycin until the full significance of toxicity and drug fastness is better known or means of avoiding them are found.

It is urged that more extensive and more adequately controlled studies be carried out to determine the possibilities and limitations of streptomycin therapy in pulmonary tuberculosis.

(6) Streptomycin therapy is suggested for further trial as a remedy for the symptoms of acute ulcerative tuberculous enteritis. Further experience will be required to define more clearly the eventual results of streptomycin treatment in this disease.

(7) Streptomycin is recommended for treatment of tuberculous draining cutaneous sinuses and appears to be highly effective in a large majority of cases, regardless of the underlying disease, except that sinuses associated with tuberculous empyema are less likely to respond to treatment.

(8) Streptomycin is not recommended for treatment of chronic empyema of tuberculous origin because of its apparent ineffectiveness in studies thus far reported.

(9) More extensive observations will be required to learn if streptomycin is of sufficient value to justify its use in (a) prophylactic treatment before and after surgical procedures, (b) treatment of tuberculosis of the genito-urinary tract, (c) treatment of tuberculosis of bones and joints, (d) treatment of tuberculosis of the skin, (e) treatment of tuberculous lymphadenitis without sinus formation, (f) treatment of ocular tuberculosis.

(10) Streptomycin, like many other useful drugs, has definite toxic potentialities. Some of these are unique and incompletely understood at the present time. The reactions listed below must be kept in mind whenever streptomycin treatment is contemplated and be compared with the hazards of the disease which is being treated.

- (a) A disturbance of vestibular function will be observed frequently especially following prolonged treatment with larger doses. Partial or complete compensation is frequently noted especially in younger individuals but the potentialities of this disorder must not be underestimated by the physician. It has not been determined if this disadvantage to streptomycin therapy can be overcome.
- (b) Deafness may be produced in very rare instances and only following large doses or

when streptomycin excretion is defective. Useful hearing is nearly always regained if treatment be suspended promptly when deafness is noted. Audiometric observations are probably advisable at this time until the conditions under which deafness occurs are better defined.

- (e) Serious renal damage produced by streptomycin appears to be observed rarely except when there is preëxisting renal disease.
- (d) Cutaneous rashes apparently due to acquired hypersensitivity to streptomycin are occasionally observed and sometimes indicate that treatment should be suspended temporarily. It is usually possible to resume treatment later. Serious exfoliative dermatitis is observed very rarely.

It has not been fully determined what the minimal effective therapeutic dose of streptomycin may be, nor is it known how dosage should be modified to secure optimal results in each of the many different types of tuberculosis. It is suggested that the total parenteral dose per twenty-four hours may be from 1.0 to 2.0 grams. It is not known how frequently intramuscular injections need be made or how long treatment should be continued. The successful results observed have usually been in patients who received injections at intervals of from four to six hours and for from three to four months. Until further studies have been concluded, it cannot be recommended that injections be made less frequently or that treatment be continued for shorter periods of time.

The disappearance of drug sensitive strains of tubercle bacilli and their replacement with strains which are drug resistant appears to offer a serious handicap to prolonged effective streptomycin therapy. It is not known as yet what conditions encourage the appearance of drug resistant organisms, how frequently this phenomenon appears, how to determine drug resistance accurately, or how permanent this change in bacterial flora may prove to be.

Streptomycin treatment should be avoided when other treatments are available because to produce a drug resistant strain of tubercle bacilli by such treatment may possibly make this form of treatment ineffective should a more serious type of tuberculosis subsequently develop.

The therapeutic trials which have been carried out by the American Trudeau Society have been made possible by contributions of streptomycin by the following manufacturers:

Merck & Company
The Charles Pfizer Company
The Abbott Laboratories

The Upjohn Company
Eli Lilly and Company
E. S. Squibb and Sons

The following investigators and their associates have been coöperating in this study:

Dr. J. Burns Amberson, Bellevue Hospital, New York City
Dr. Emil Bogen, Olive View Sanatorium, Olive View, California
Dr. H. Corwin Hinshaw, (*Chairman*), Mayo Clinic, Rochester, Minnesota
Dr. Kirby S. Howlett, Jr., Laurel Heights Sanatorium, Shelton, Connecticut, and
Yale University
Dr. Walsh McDermott, New York Hospital, Cornell University, New York City

Dr. E. N. Packard, Trudeau Sanatorium, Trudeau, New York

Dr. H. McLeod Riggins, Lenox Hill Hospital, New York City; Biggs Memorial Hospital, Ithaca, New York; Mount Morris Hospital, Mount Morris, New York; Homer Folks Hospital, Oneonta, New York; Ray Brook, Saranac, New York

Dr. H. Stuart Willis, Maybury Sanatorium, Northville, Michigan, and North Carolina State Sanatorium, Sanatorium; North Carolina.

Extensive studies are under way to define further (1) the possible applications of streptomycin therapy in tuberculosis; (2) the optimal methods of using the drug with minimal discomfort and expense; (3) the clinical significance of acquired drug resistance on the part of tubercle bacilli and possible methods of preventing this phenomenon from occurring; (4) the combination of streptomycin with other therapeutic drugs; and (5) the toxicity of streptomycin and possible methods of minimizing these effects.

The development of an effective antibiotic agent against tuberculosis *which is not universally applicable* will surely complicate the practice of medicine as it relates to tuberculosis. It will be of increasing importance that tuberculosis be treated by physicians whose knowledge of the disease is sufficiently broad to permit them to choose wisely which patients should assume the discomforts, the risks and the expense of utilizing this incompletely explored type of therapy.

Streptomycin alone does not appear to be adequate to arrest those types of pulmonary tuberculosis which are most likely to be treated effectively by major surgical procedures. It is not considered safe to permit streptomycin therapy to substitute for bed-rest treatment. It is further recommended that effective streptomycin treatment be followed and supplemented by adequate rest therapy because of the serious risk of exacerbation of the disease process after conclusion of treatment. Such exacerbations may fail to respond to second courses of therapy.

It is emphasized in strongest terms that streptomycin cannot be regarded at this time as a satisfactory substitute for therapeutic methods which are already known to be effective for pulmonary tuberculosis. Hope is entertained that it may be a valuable supplement to such methods of treatment. The need for continued research is most urgent.

Report of the Laboratory Subcommittee on Streptomycin
Subcommittee of the Committee on Therapy

Laboratory Subcommittee on Streptomycin

Dr. Guy P. Youmans, *Chairman*

Dr. Emil Bögen

Dr. C. Eugene Woodruff

Dr. H. Corwin Hinshaw

Mr. William Steenken (NTA)

The Laboratory Subcommittee on Streptomycin held a one-day meeting on Friday, November 29, 1946, in New York City. At this meeting the Committee

discussed the laboratory controls that would be necessary in the proposed clinical investigation of the effect of streptomycin on tuberculosis, and the laboratory facilities that would be necessary to adequately cover such a program.

It was agreed by the Committee that members of the original group of investigators on the streptomycin committee should set up laboratory facilities for the study of tubercle bacilli isolated from patients and that one or more central laboratories be established to explore these problems in greater detail. Also that the Committee should consult among its members regarding methods of studying the sensitivity of tubercle bacilli to streptomycin and that the Committee make recommendations as to the procedures and techniques to be used.

It was felt by the Committee, since the development of resistance of tubercle bacilli to streptomycin during treatment was one of the most important factors in the successful outcome of therapy, that:

- 1: Cultures of tubercle bacilli should be isolated from all patients prior to the institution of streptomycin treatment.
- 2: Cultures of tubercle bacilli should be isolated from all patients under streptomycin treatment, if possible, at weekly intervals following the institution of streptomycin treatment.
- 3: The streptomycin sensitivity of these cultures should be tested at periodic intervals and those cultures isolated but not tested should be stored for further study.

In order to facilitate the study of streptomycin resistance of tubercle bacilli it was decided that three central laboratories be established with funds to be provided by the National Institute of Health. These laboratories would be located at:

1. Trudeau Sanatorium, Trudeau, New York
Supervised by Mr. William Steenken
2. Northwestern University Medical School, Chicago
Supervised by Dr. Guy P. Youmans
3. Olive View Sanatorium, Olive View, California
Supervised by Dr. Emil Bogen

and the functions of the central laboratories would be:

- 1: Upon request to determine the streptomycin sensitivity of cultures from any of the affiliated laboratories.
- 2: The storage of cultures of tubercle bacilli for future study.
- 3: The training of laboratory personnel if requested.
- 4: To serve in a supervisory capacity upon request.
- 5: To carry on fundamental research on the chemotherapy of tuberculosis.

The Committee decided it would be advisable to recommend procedures for:

- 1: The determination of the sensitivity of tubercle bacilli to streptomycin.
- 2: Methods of preservation of tubercle bacilli.
- 3: Methods for the determination of streptomycin blood levels.

and that this information be put together in mimeographed form so it would be available upon request to interested parties. Furthermore, it was decided that the central laboratories should collaborate when necessary for the purpose of determining the most suitable methods for the above procedures. The outline of recommended procedures has been completed following extensive correspondence and is now available.

Upon the recommendation of Dr. H. C. Hinshaw, a suggested labeling system for cultures of tubercle bacilli to be sent to the central laboratories has also been included in the outline.

It is recognized by the Committee, however, that considerable work is necessary to determine the best method for the preservation of tubercle bacilli and for the determination of streptomycin blood levels. Furthermore, in view of recent information, supplied by Lt. Fisher of Fitzsimons General Hospital, Denver, Colorado, indicating that the methods now in use for the testing of the sensitivity of cultures of tubercle bacilli to streptomycin give discrepant results, the Committee, in collaboration with the central laboratories, and with Dr. Alfred G. Karlson of Mayo Clinic, Rochester, Minnesota and Lt. Fisher of Fitzsimons General Hospital, Denver, Colorado, has outlined a program to determine which of the methods now in use is the most reliable and, if necessary, attempt to devise a more suitable method.

Report of the Subcommittee on Thoracic Surgery
Subcommittee of the Committee on Therapy

Subcommittee on Thoracic Surgery

Dr. Richard H. Meade, Jr., *Chairman*

Dr. John C. Jones

Dr. Richard H. Overholt

Dr. Herbert C. Maier

Dr. John D. Steele

Dr. Richard H. Sweet

The Subcommittee on Thoracic Surgery wishes to report that the investigation it undertook to determine the present status of pulmonary resection, and of extrapleural pneumonolysis, in the treatment of pulmonary tuberculosis has not been completed. Questionnaires have been sent out to the men doing this work and while many answers have been received the number is far too small to justify any conclusions.

It is recommended that the investigation be continued through the coming year, either by the present Committee or by a new one.

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ABSTRACTS

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Tuberculosis Control.—There are three kinds of approaches to tuberculosis control, advocated by different groups: (1) the single technique of examining contacts of known cases, believed to discover all the new cases in the community; (2) an annual tuberculin test of every person as the sole means of discovering all cases of tuberculosis; (3) a total assault by (a) community-wide X-ray surveys done within a deliberately limited period of time, (b) adequate follow-up facilities and examination of contacts of previously known and newly discovered cases, and (c) tuberculin testing of samples of a population at stated intervals. However, careful studies have shown that examination of contacts discovers only about 25 per cent of new cases reported each year. In such a program the important principle of examining the adult population in a limited time cannot be effective, and intense and continuous exposure of the public to hidden cases will occur. Annual tuberculin testing of the entire population with X-ray examination of reactors is impracticable. In large cities the major part of the adults are reactors; so, little is gained by tuberculin testing before X-ray examination. This test is most efficient in establishing the diagnosis of tuberculosis after X-ray examination. It is, furthermore, useful in determining changes in the infection rate from year to year, when applied to sample groups of the community, and it might be desirable, after isolation of spreaders of the disease and supervision of contacts, to test those whole communities where the infection rate is low. The Tuberculosis Control Division of the United States Public Health Service, by means of some demonstration units for assisting selected cities, can show that even the larger population groups in the country can be surveyed in less than three years. With the

help of tuberculosis associations and local medical societies every community can develop time-plans for tuberculosis control. The large and small communities of the entire United States could be covered by mass radiography teams in less than five years' time.—*The Time Element in Tuberculosis Control*, H. E. Hilleboe, *Pub. Health Rep.*, June 6, 1947, 62: 825.—(O. Pinner)

Family Protection in Uruguay.—A law adopted in Uruguay in January, 1946 provides that any worker suffering from tuberculosis must give up his work until cured, the Government undertaking to support his family in the meanwhile. The expenses involved are borne by a National Tuberculosis Fund which so far has proved ample for the purpose. This includes the proceeds from a national collection and a tax on popular amusements. Family pensions are granted for a six-month period and are renewable. The amount depends on various factors, and especially the health and economic situation of the family, varying up to now between 10 and 100 pesos a month. These pensions are allotted under the following conditions: medical care and hospitalization of the patients in one of the Government tuberculosis hospitals; medical examination and supervision of the family; and study of the financial condition of the household.—*Aspectos de la gestión de la Comisión Honoraria para la Lucha Antituberculosa*, A. Fernández, *Hoja tisiol.*, March, 1947, 7: 29.—(A. A. Moll)

Adult Tuberculosis in Childhood.—Latent lesions in childhood may represent primary foci, localized consolidations or small nodules resulting from the secondary hematogenous dissemination of Ranke. Tertiary lesions are also held to be usually of endogenous origin,

due to reactivation of a latent primary lesion in the lower parts of the lung, or more often from secondary lesions in the upper parts of the lungs, although exogenous reinfections may exist. Air-borne exogenous reinfections should localize in the lower parts of the lungs since the endobronchial aerial mechanics are the same in allergic and nonallergic subjects. Five instances of bilateral apical lesions in adolescents with healthy parents are cited as evidences of endogenous dissemination.—*Pathogénie de la tuberculose tertiaire de l'enfant et de l'adolescent*, A. Vaquette & G. Boutin, *Presse méd.*, February 15, 1947, 55: 111.—(E. Bogen)

Tuberculosis in Diabetes.—During the nineteenth century, with the incidence and mortality of pulmonary tuberculosis much higher than at present, about 50 per cent of those diabetics who survived died of pulmonary tuberculosis. Even with the introduction of insulin, the incidence of tuberculosis in diabetics has remained high. Seventeen cases of diabetes mellitus and tuberculosis encountered during the supervision of 717 patients suffering from diabetes during the period of 1932-1946 are reviewed. There were 60 deaths, 11 from pulmonary tuberculosis. In 11 of the 17 cases, diabetes preceded the onset of tuberculosis by periods up to thirteen years, while in the other 6 cases the diagnosis was made simultaneously. In the greater percentage of cases, tuberculosis made its appearance in the fifth decade, whereas the majority of cases of tuberculosis in the general population occur in the second or third decade. This suggests that tuberculosis developed on account of preëxisting diabetes mellitus. Tuberculosis is more prone to be a complication in the uncontrolled diabetic. The most frequently accepted hypothesis is that hyperglycemia favors the growth of the tubercle bacillus in the body. Hyperglycemia may impair the normal reparative tissue processes and the resistance to infection. However, an upset in fat metabolism with an increased availability of glycerin may be a factor. Diabetic coma, with an oversupply of nitrogenous compounds, which favor the growth of the tubercle

bacillus, may cause a pulmonary focus to flare up. Acidosis may be a factor in increasing the virulence of the tubercle bacillus. Vitamin-A deficiency, combined with fat metabolism in the diabetic, may be another factor playing a part in the unfavorable association of diabetes and tuberculosis. It is felt by some that the controlled diabetic has about the same chance of survival as the nondiabetic with comparable therapy for pulmonary tuberculosis. In the present series of 17 cases, 11 are dead, 7 within the first year, 3 within the second year and one within three years. In 2 cases the cause of death was coronary thrombosis, and in these cases the chest condition was stationary. Another death was due to pulmonary embolism in a patient whose chest condition was unsatisfactory. Of those still alive, 3 are in the critical phase of the first two years, which are well recognized as carrying the highest morbidity. It is urged that early diagnosis and adequate treatment for both tuberculosis and diabetes be recognized as the best solution to this difficult problem.—*Tuberculosis as a Complication of Diabetes Mellitus*, W. R. Gauld & A. Lyall, *Brit. M. J.*, May 17, 1947 4506: 677.—(R. W. Clarke)

Rehabilitation.—There is still no widespread acceptance of rehabilitation, although rehabilitation and after-care of all tuberculous persons, beginning at the moment of diagnosis and continuing after as long as five years after release from the sanatorium, is one of the essentials in a sound program of tuberculosis control, important for the maintenance of the newly acquired health of the patient, as well as for the protection of the community from prolonged material liabilities. There is urgent need to acquaint the medical profession, not excluding some sanatorium physicians, with the rôle they should play in this task. The clinician alone has opportunities for observing the physical, intellectual and personal patterns of the patient. After the arrest of the disease, the vocational counselor and the medical social worker have to decide how to provide training, guidance and appropriate employment. Course units in the whole field of rehabilitation

should be established in every medical school and practical courses should be included in graduate schools. They should be supplemented by: (1) research in the psychology of the tuberculous; (2) study of the capacity of the tuberculous for types and quantity of work; (3) analysis and evaluation of present knowledge of the psychic patterns of human beings in general. Find, treat, rehabilitate the tuberculous: this trinity of approach means unity and total attack.—*Rehabilitating the Tuberculous*, H. E. Hillboe, *Pub. Health Rep.*, July 6, 1947, 62: 969.—(O. Pinner)

Demonstration of Tubercle Bacilli.—This is an abstract of a paper by J. Holm and Vera Lester, published in *Aeta tuberculosa Scandinavica*, 1941, 16, 3. From June 1, 1938 to February 28, 1941, 20,090 specimens of various kinds were tested simultaneously by culture and guinea pig inoculation; 3,731 specimens were positive; 3,273 were of the human and 458 of the bovine type. While culture failed in 323 instances (8.6 per cent) the guinea pig test failed in 829 (22.2 per cent). Culture is considerably more sensitive on the whole than guinea pig inoculation. However, the latter test is superior for the demonstration of the bovine tubercle bacillus: inoculation failed in 56 (12.2 per cent) of the 458 bovine positive specimens, culture failed in 76 (16.6 per cent). Culture failures occurred in 7 per cent of the guinea pig positive gastric lavages, 4 per cent of sputa, 10 per cent of the pleural exudates, 6 per cent of spinal fluids, 15 per cent of urines, 7 per cent of pus, tissue, etc. The success of inoculation depends largely upon whether the inoculum is homogenized. Specimens used for inoculation were tested in the native state unless judged to contain numerous microbes pathogenic for animals. Nearly all specimens were homogenized for culture, although this procedure damages the organisms. The greater the bacillary content of the culture, estimated from the colony count, the greater was the probability of a positive guinea pig test. Each specimen was equally divided for inoculation and culture; it might be assumed that absence of tubercle bacilli from the por-

tions used for inoculations was responsible for the increasing failures as the bacillary content decreases. This is hardly acceptable when the amount of increase is considered. A certain minimal amount of bacilli capable of propagation is required for the production of tuberculosis in guinea pigs. This number probably depends on several conditions. The initial virulence, the degree of attenuation by homogenization, and the variable resistance of the guinea pigs are important. A total of 136 guinea pigs died from causes other than tuberculosis, mostly infection with type 19 pneumococci and more frequently in winter and spring when their resistance was lowered by a less sufficient diet. This dietary change did not alter the resistance of the guinea pigs to infection with tubercle bacilli. It is concluded that the guinea pig test could safely be omitted for a large proportion of specimens; it is used now only for a few kinds of specimens. Differentiation of cultures of tubercle bacilli and saprophytes is difficult, and even the expert must sometimes resort to testing doubtful colonies on guinea pigs, preferably by intracutaneous inoculation. Culture is more economical than inoculation; typing is made possible through direct observation of the colonies and a positive diagnosis can be obtained in three or four weeks, against six weeks with the guinea pig test. The method employed for culture is described in detail.—*Diagnostic Demonstration of Tubercle Bacilli (An Abstract, see beginning)*, *Pub. Health Rep.*, July 6, 1947, 62: 47.—(O. Pinner)

Normal Sedimentation Rates in Active Tuberculosis.—Normal sedimentation rates were found in 20.8, 34.6 or 36.9 per cent of active cases, depending on the criteria used to determine activity of the disease, in 1,066 cases of active pulmonary tuberculosis admitted to the Sampson Naval Hospital. The test, however, continues to be of value in this disease if used with careful regard for its limitation.—*Normal Sedimentation Rates in Active Pulmonary Tuberculosis: A study of 1,066 Cases in a Naval Tuberculosis Center*, T. H. Noehren, *J. Lab. & Clin. Med.*, May, 1947, 32: 526.—(F. G. Petrik)

Pulmonary Calcification in Montevideo.—

Postmortem examinations were made in 100 persons, 4 days to 90 years old, who died in accidents in Montevideo. Gross and microscopic studies supplemented by X-ray examination showed in 19 per cent "slate-like" pneumonic processes and in 25 per cent pleural adhesions. In most cases, these were apparently not tuberculous. In 2 children, 20 months and 3 years old, and in 2 adults active progressive tuberculosis was found. In 10 per cent of the group, mostly in persons over 40, caseous reinfection lesions were present. Calcifications of an obvious tuberculous nature in the lung or lymph nodes existed in 94 per cent of the whole series and in 100 per cent of patients over 21. Where various calcareous deposits occurred, histological study revealed that the infections had taken place at intervals of years and were exogenous. In some cases, calcified masses without nodal involvement preceded the development of manifestations in the nodes and lungs. The presence or absence of enlarged nodes is therefore not sufficient to establish whether a process is primary or secondary. These small recurring lesions may explain the development and maintenance of allergy. (In Montevideo surveys so far made show that among persons about 20 years old, 85 per cent and, at 35, 98 to 100 per cent are tuberculin-positive.) —*Frecuencia de las calcificaciones ganglionares entre los habitantes de Montevideo*, F. D. Gómez & J. J. Scandraglio, *Hoja fisiol.*, March, 1947, 7: 1.—(A. A. Moll)

Tuberculous Hilar Node Enlargement in Adult.—Two cases of tracheobronchial lymph node tuberculosis are reported, one in a patient with primary infection and the other in a patient already allergic to tuberculin. The first case rapidly developed a typical early infiltrative in the lung parenchyma, below the interlobar fissure, but under rest treatment improved rapidly, while at the same time the tracheobronchial nodes diminished in size. Such cases are rare in adult life, even in patients with primary infection, as the lymphatic tissue of the adult is said to have much less

capacity for reaction than that of the child. The author is inclined to classify the case as one of rapid progression from the initial lesion to the third stage of Ranke, the full-blown phthisis of adolescence, with only transitory second-stage manifestations. Ordinarily the cases of primary infection with rapid node involvement have been serious ones with fatal termination. Such cases occur in individuals with little native resistance to tuberculosis, and in persons such as many in Western Europe to-day who have lost all resistance to the disease. The second case was that of an already infected patient with a positive tuberculin reaction who developed the usual signs of symptoms of pulmonary tuberculosis of the adult type and whose X-ray film showed in addition a rounded, homogeneous, sharply defined shadow adjacent to the trachea on the right side, interpreted as representing enlargement of a single chain of mediastinal nodes. He was given rest treatment and eventually the nodal shadow entirely disappeared. These cases the authors consider exceptions to the dictum of Rist and Ameiulle (*Bull. et Mém. Soc. Méd. Hôp.*, Paris, April, 1914, p. 651) that tuberculosis in the adult is not usually accompanied by tracheobronchial lymph node involvement. However, such cases are unusual even in patients who develop a primary infection in adult life.—*A propos de l'adénopathie trachéobronchique tuberculeuse chez l'adulte*, P. Mannes & R. Priest, *Le Poumon*, January-February, 1947, 3: 55.—(A. T. Laird)

Tuberculous Pericarditis.—Pericardial effusion caused by tuberculosis has always been considered a rare condition with a high mortality. It is difficult to distinguish an effusion caused by tuberculosis from one caused by rheumatic fever. Diagnosis at times has to be presumed to be tuberculous only by the presence of other tuberculous manifestations, or by the absence of signs indicative of rheumatic origin. Characteristics of tuberculous pericardial effusion are: (1) no enlargement of the heart, (2) no gross murmurs or murmurs indicative of valvular enlargement, (3) no rheumatic manifestation, (4) no past or family

history of rheumatism. In addition, there is no marked anemia, an insidious onset, no leucocytosis, and, although the effusion may be large, the symptoms, especially precordial pain, are not marked. To have the pericardium as the sole site of tuberculous infection is rare. Pericardial effusion as the first clinical manifestation of active tuberculosis is not so uncommon. It seems generally agreed that the pericardial sac is relatively immune in a general miliary spread, and it appears that, if miliary spread is present, it is probably subsequent to a pericardial lesion. Tuberculous pericarditis is often shown to have followed involvement of the mediastinal lymph nodes and is spread through the lymphatics. Once the pericardium becomes infected, there follows an effusion with cardiac embarrassment lasting for several months, succeeded by phases of decreasing effusion with temporary recovery and finally increasing thickening and fibrosis of the pericardium, leading to congestive failure and death. However, there may be recovery from a transient effusion, with absorption of the fluid, giving rise to no residual signs or symptoms of pericardial involvement. Four cases of pericardial effusion are described, one in an infant of 18 months. It is suggested that tuberculous pericardial effusion may be a more common condition than has been previously recognized, that it may be insidious in its onset, transient in its course and complete in resolution.—*Tuberculous Pericarditis*, H. Kopelman, *Brit. M. J.*, April 26, 1947, 4503: 559.—(R. W. Clarke)

Atypical Abdominal Tuberculosis.—Typical abdominal tuberculosis includes cases of (1) abdominal primary complex, (2) tuberculosis of the peritoneum in the course of hematogenous tuberculosis and (3) intestinal tuberculosis. This paper deals with cases illustrating four atypical forms. (1) Fulminant tuberculous septicemia with spread of miliary or larger foci of tissue necrosis chiefly or exclusively in the abdominal organs: The illness was of four weeks' duration. There was extensive involvement of the spleen, liver and mesenteric nodes. The chest organs were free

of involvement. There was a severe leucopenia resulting from bone marrow involvement. The portal of entry was probably the intestine. (2) Unusual distribution and changes involving abdominal organs, such as large tuberculomata restricted to the spleen, liver, nodes or biliary tract: The patient had a febrile illness four months prior to death from tuberculous meningitis. Necropsy revealed primary abdominal tuberculosis. There was extensive caseation of the abdominal nodes. No such changes were found in the chest. There was a caseous cholangitis with intratubular extension to the liver. The portal of entry was thought to be the duodenum. (3) Tuberculosis of the abdominal lymphatic system secondary to old primary infection of the lung: There was a fresh exacerbation in the glandular component of the thoracic complex. The infection extended by way of the posterior mediastinal nodes to the periaortic and periportal nodes. The peritoneal serosa and omentum were grossly involved by lymphatic spread. (4) Hematogenous spread in the liver and spleen or both with cavitation: In this case there was cavitation in a splenic nodule.—*Fulminant Tuberculous Septicaemia and Other Atypical Forms of Abdominal Tuberculosis*, E. J. Blair & W. Pagel, *Tubercle*, June, 1947, 28: 115.—(A. G. Cohen)

"Reticulotropic" Tuberculosis.—Two prisoners repatriated from Germany are described in whom fatal, rapidly progressive, pulmonary tuberculosis was associated with wide-spread tuberculous lymphadenopathy, especially cervical and mediastinal, and with changes in bone marrow, liver or spleen. Although autopsies were not obtained, biopsies during life showed wide-spread caseation of the lymph nodes and marked changes in the reticulo-endothelial system suggestive of Hodgkin's disease or acute mononucleosis.—*La tuberculose réticulotrope, Forme maligne de la tuberculose ganglionnaire*, P. Cazal, *Presse méd.*, February 8, 1947, 55: 99.—(E. Bogcn)

BCG and Tuberculin Sensitiveness.—Three hundred and seventy-seven persons 2 to

68 years old who were all Mantoux-negative (1:10) were inoculated intracutaneously with 0.1 mg. of killed BCG. Tuberculin allergy was revealed in 104 (27.6 per cent). This allergy expressed itself in the form of an early nodule over 6 mm. in diameter in the inoculation site; occurrence of the Willis-Sayé phenomenon (early development of general allergy); and delayed tuberculin positivity. The characteristic nodular reaction is the main and most reliable guide, it being found in 100 per cent of the cases. The Willis-Sayé sign is not so consistent (69 out of 104 cases). Delayed positivity is sporadic (seen only in 13 cases). In nonallergic cases the nodule never exceeds 5 mm. in diameter and the Willis-Sayé phenomenon does not occur. This BCG allergy persisted throughout the observation period in about 75 per cent of 34 cases studied. The extinction of tuberculin sensitiveness is an unquestionable fact and the usual concept of tuberculin allergy developing as a result of a primary infection is no longer tenable. Its disappearance, however, does not necessarily mean an immediate return to a nonallergic condition. Tuberculin sensitiveness means a greater resistance to superinfection. Tuberculin allergy may be found in cases of tuberculous disease with a favorable outlook. The use of BCG in the determination of tuberculin allergy has the advantages derived from a stable antigen and lacks the disadvantages connected with the introduction of live organisms in the body. It provides also a most sensitive and accurate test.—*Contribuição ao estudo da alergia infratuberculínica, J. Rosenberg, Rev. brasil. de tuberc., September-October, 1946, 15: 527.*—(A. A. Moll)

Pneumothorax.—At an institution where about 3,000 pneumothorax refills are given each year, 6 cases of intrapleural hemorrhage occurred in three years; this was an incidence of 1 in 2,500. In 5 cases, there was a free pleural space without adhesions. In 3 cases, pain occurred during the refill; in all cases pain was noted later in the day. Since the needles are inserted routinely close to the lower margin of a rib, trauma to an intercostal nerve

was regarded as an unlikely cause of the pain. There was no malaise. In 4 cases fever was noted within three days. Treatment consisted of immediate aspiration followed by irrigation with saline until a clear return was obtained. Subsequently, following daily fluoroscopic observation, aspiration and irrigation were done as indicated. In 4 cases only one aspiration was required. If the first aspiration was performed within forty-eight hours, the pneumothorax space was not lost. The bleeding probably comes from vessels beneath the parietal pleura. Pain on insertion of the needle should arouse suspicion of bleeding.—*Intrapleural Hemorrhage following Artificial-Pneumothorax Refills, A. K. Miller & R. J. Rinkel, Lancet, June 28, 1947, 1: 907.*—(A. G. Cohen)

Pleural "Mice".—For a dozen years the author has been noting sharply limited shadows in the pleural cavity during pneumothorax treatment. These sometimes seem to have rhythmical movement synchronous with the heart beat, and often seem to be attached as appendices of moderate density to the lower pole of the collapsed lung. Occasionally they are in the pleural cavity, the so-called pleural "mice;" at other times they may be confused with pleural adhesions, but always situated at the lower extremity of the lung. Many other observers have doubtless observed these same densities but have not considered them of any special importance, nor does the author think they present any special diagnostic or therapeutic problem. However he has been curious about them, and in 1939 his colleague, F. Declercq, published a short report of instances observed in the Hospital St. Pierre in Brussels (Le Scalpel for July, 1939), hoping to follow it by pathological reports should there be any opportunity for postmortem study of such bodies. No such histological studies have yet been reported, and the author admits that his conclusions regarding their nature lack confirmation. According to Declercq, they are quite common and are to be found in nearly half of all films of pneumothorax in which the lower border of the lung is visible. The

author's explanation is that the diaphragmatic pleura and the parietal pleura, normally in contact in the costophrenic angle, actually contain a potential space which fills with fluid in the early stages of pneumothorax treatment. This is usually absorbed later, or if it remains it does not show any tendency to increase. One would hesitate to call it a pleural effusion, it is so trifling in amount. The withdrawal of the collapsed lung from the diaphragm may be considered a traumatic interference with the normal relations of the pleural surfaces and thus an irritation. The injected air must also be considered an irritant. At any rate, fluid accumulates in certain cases, drop by drop, in the costophrenic angle; the irritated pleura in this angular area, into which the collapsed lung is forced, exudes inflammatory serous fluid, and the fibrinous deposit becomes opaque and radioscopically visible. When the lung point, due to its retractility, eventually is drawn away, there is sometimes attached to it an appendage having the precise contour of the angle. At other times there are adhesion-like strings attached, but these are often free and move freely in the effusion if one has developed. They may have become attached to the opposite pleural wall or in other cases detached and form the so-called pleural "mice." The S films in which these densities have been noted leave much to be desired in their reproduction. [Densities such as those described by the author are occasionally seen in pneumothorax in the United States, and his explanation of their formation from fibrinous deposits about a nidus (possibly of blood?) on the pleural surface is probably correct. It would be difficult to confirm his theory that they usually occur first only at the lower edge of a collapsed lung in the costophrenic angle.]—*Condensations polaires inférieures observées au cours des pneumothorax thérapeutiques*, J. André, *Le Poumon*, January-February, 1947, 3: 47.—(A. T. Laird)

Results of Phrenicectomy.—A series of 122 patients treated for pulmonary tuberculosis by phrenicectomy between the years 1926 and 1945 is presented: 82 (67 per cent) died; 11

(9 per cent) are still under observation; 7 of the latter have been clinically cured and have been leading a normal life for more than ten years; 29 patients (24 per cent) were lost sight of. However, 10 of those had been followed up over five and up to sixteen years. The corrected statistics prove that, of 103 followed-up patients, 15 (5 per cent) were clinically cured, 6 (6 per cent) were stationary and 82 (80 per cent) had died; 29 patients died within one year after phrenicectomy. Only 4 of the deaths were not attributable to tuberculosis. In 75 cases, phrenicectomy was the only treatment; 47 patients received additional treatment: pneumoperitoneum (4), pneumothorax (16), thoracoplasty (13), thoracoplasty and pneumothorax (14). The higher the diaphragm ascended, the more unfavorable was the prognosis and the greater was the early mortality. The best results were obtained with complete immobilization and a slight to moderate elevation of the hemidiaphragm. There was no difference in the results for patients with or without cavities. Favorable results are attributed to the self-healing tendency in many cases of tuberculosis. On the basis of these experiences, the treatment of tuberculosis with phrenicectomy alone cannot be encouraged. It should not be substituted for other types of collapse therapy.—*Veinte años de experiencia en el tratamiento de la tuberculosis pulmonar por la frenicotomía*, F. D. Gomez, J. C. Negro & R. Burgos, *Hoja fisiol.*, March, 1946, 6: 36.—(W. Swienty)

Intracavitary Drainage.—Fifteen cases are reported in which Monaldi drainage was used. In 8 of them no permanent improvement was secured and the patients died after a downhill course. Three have secured a clinical cure which the passage of time has confirmed, 2 others have improved but cannot be considered completely cured, while 2 others still under treatment have a favorable prognosis. From this experience it is concluded that the method should not be used in cases where the cavities are of long standing and have stiff fibrous walls. Under such conditions, even though slight reduction in the size of large cavities

is obtained, healing of the walls and permanent contraction and disappearance of the cavity are impossible. Proximity of the cavity to pleural adhesions is unfavorable for healing. Cavities in lung tissue which contains disseminated nodular lesions surrounded by emphysema are not susceptible of adequate drainage and healing. Multiple cavities in the same lobe constitute a contraindication to the method. Laryngeal tuberculosis does not make it inadvisable. The external drainage of a cavity is usually not indicated unless the measure is supported and supplemented by collapse therapy. Used in connection with other surgical procedures, Monaldi drainage may render later surgery less extensive, and so preserve intact healthy lung tissue, especially at the base of a lobe. To avoid serious infection of the fistula formed where the drainage is introduced, the author advises, in the case of an apical cavity, preliminary resection of a portion of the first and second ribs. Cavities practically never become effaced without thoracoplasty but in certain cases thoracoplasty may be less extensive if drainage is used. Large cavities are prone to be accompanied by serious contralateral lesions requiring preliminary collapse therapy. Monaldi's method should be restricted to the relatively rare cases of recent localized cavitation with relative integrity of the other lobes. By its use some patients whom it would otherwise seem necessary to abandon to purely symptomatic treatment may be benefited.—*Quelques considérations au sujet de l'application de la méthode de Monaldi en tuberculose pulmonaire, J. Wins, Le Poumon, January-February, 1947, 3: 88.*—A. T. Laird)

Postural Treatment.—The "lying down slanting treatment" requires only a *chaise-longue* and a few blocks or bricks in the open air. No pillow is allowed and dorsal or lateral decubitus are the only positions permitted. At first the bed is horizontal but gradually the sloping position is increased by bricks under the front legs of the chair until a slight Trendelenburg position is achieved. Presence of effusion and tuberculosis of both bases are

contraindications. No discomfort has been reported although a few restless patients complain of the prolonged immobilization. This treatment is usually associated with phrenicectomy, pneumothorax or gold therapy. In single upper lesions, homolateral decubitus is the rule. In a single basal lesion a phrenic operation should precede the cure. When both apices are involved dorsal decubitus is indicated. The treatment has been used for several years in many patients with unquestionable success. It has also the advantages of its low cost and applicability at home.—*La cura de declive en el tratamiento de la tuberculosis pulmonar, P. Nemirowsky, Rev. de tuberc. d. Uruguay, March, 1946, 14: 7.*—(A. A. Moll)

Streptomycin Toxicity.—In order to evaluate the chronic toxicity of streptomycin, 16 patients with active pulmonary tuberculosis were treated with highly purified streptomycin sulfate. They received 3 g. of streptomycin daily, administered at three hourly intervals for a period of at least 120 days. There was remarkably little irritation at the site of the intramuscular reaction. Two patients developed manifestations of anaphylaxis. The treatment could be resumed in both patients after an interval of several weeks. Fourteen patients developed eosinophilia at some time during the course of the treatment. Cylindruria appeared in 14 patients, in 10 of them it occurred within forty-eight hours of the institution of therapy. When the urine was kept at a neutral or slightly alkaline pH cylindruria was demonstrable in only one patient. Reduction in renal function appeared in only 2 patients and in one of these the restoration of normal function occurred despite the continued administration of the drug. Symptoms of vestibular dysfunction appeared between the seventeenth and twenty-fifth days of therapy in all 16 patients. Complete symptomatic recovery occurred in all subjects. Two patients developed deafness, both had received streptomycin intrathecally for the treatment of tuberculous meningitis. Repeated intrathecal administration of not more than 0.1 g. of strep-

tomyacin to patients without evidence of central nervous system disease was well tolerated. Larger amounts produced untoward reactions at times. There was no so-called histamine reaction in the entire group.—*Streptomycin Toxicity: Reactions to Highly Purified Drug on Long-continued Administration to Human Subjects*, R. F. Farrington, Harriet Hull-Smith, P. A. Bunn & W. McDermott, J. A. M. A., June 21, 1947, 134: 679.—(H. Abeles)

Oxygen Consumption.—Among 335 cases of various types of pulmonary tuberculosis, in 76 (22.6 per cent) respiratory difficulty was evidenced at rest, as shown by the increased oxygen consumption when this gas was introduced to replace the air in the circuit used. In 132 cases (39.4 per cent) oxygen consumption decreased under the same conditions, and in 127 (37.9 per cent) no changes occurred. Knipping has already commented on this phenomenon and explained its compensatory character in tuberculosis. Patients with a weakened neuromuscular system increase their oxygen consumption under basal conditions.—*El consumo de oxígeno en la exploración funcional del aparato respiratorio*, R. Burgos, Hoja fisiol., March, 1947, 7: 49.—(A. A. Moll)

Respiratory and Circulatory Responses to Oxygen.—The respiratory and circulatory responses of 81 normal individuals to the inhalation of 100 per cent oxygen and 18, 16, 14.5, 12, 10 or 8 per cent oxygen in nitrogen have been studied. An immediate decrease in pulse rate or respiratory volume occurred in 28 of 33 subjects when inhalation of 100 per cent oxygen followed room air. This suggests that some chemoreceptors of the carotid and aortic bodies are tonically active at the oxygen tension present in the arterial blood of many normal men breathing room air at sea level. An increased minute volume of respiration was noted in only a few individuals breathing 18 per cent oxygen, the majority showing no significant change until 16 per cent oxygen was inhaled. The respiratory response to anoxia was characterized by extreme individual vari-

ability and by the fact that only slight stimulation was noted until 10 or 8 per cent oxygen was inhaled. The response of the circulatory system to anoxia differed markedly from the respiratory response. Significant increase in pulse rate occurred when the concentration of oxygen in the inspired air was reduced from 20.9 to 18 per cent. Progressive increases in pulse rate accompanied further reduction in inspired oxygen concentration. Additional evidence of the respiratory stimulant action of 100 per cent oxygen was obtained. Bradycardia and a reduction of cardiac output per minute were noted simultaneously under these conditions. The wide range in arterial oxygen saturation described by others for individuals breathing the same low oxygen mixture was confirmed. (Authors' summary).—*The Effect, of the Inhalation of High and Low Oxygen Concentrations on Respiration, Pulse Rate, Ballisto-cardiogram and Arterial Oxygen Saturation (Oximeter) of Normal Individuals*, R. D. Dripps & J. H. Comroe, Jr., Am. J. Physiol., May, 1947, 149: 277.—(G. C. Leiner)

Carbon-dioxide Inhalation.—The average volume of respiration of 42 subjects inhaling 7.6 per cent carbon dioxide in oxygen was 51.5 liters per minute. The average minute volume of respiration of 31 subjects inhaling 10.4 per cent carbon dioxide in oxygen was 76.3 liters. Pulse rate and blood pressure rose under carbon-dioxide inhalation. In 19 subjects the average maximal ventilation produced by inhalation of 7.6 per cent carbon dioxide was 48.9 liters per minute; by inhalation of 10.4 per cent, 71.4 liters per minute; by muscular exercise, 109.6 liters per minute; by voluntary hyperventilation (maximal breathing capacity), 166 liters per minute. The most frequent symptoms produced by inhalation of carbon dioxide were headache, dizziness and dyspnea.—*The Respiratory and Circulatory Response of Normal Man to Inhalation of 7.6 and 10.4 Per Cent CO₂ with a Comparison of the Maximal Ventilation Produced by Severe Muscular Exercise, Inhalation of CO₂ and Maximal Voluntary Hyperventilation*, R. D.

Dripps & J. H. Comroe, Jr., Am. J. Physiol., April, 1947, 149: 48.—(G. C. Leiner)

Respiration and Vagal Stimulation.—Under urethane anesthesia low frequency central vagal stimulation in dogs caused respiratory acceleration. High frequency stimulation continuously or during expiration slowed the breathing by prolonging the expiratory phase, unless the duration of the stimulus was limited so that only a small number of shocks was applied, when respiratory acceleration occurred. Acceleration was also caused by high frequency afferent vagal stimulation during inspiration, that is, by intermittent inspiratory inhibition analogous to the lung-stretch reflexes. Under barbiturate anesthesia respiratory acceleration with low frequencies of vagal stimulation usually failed to occur, and these stimuli usually inhibited the breathing. Vagal stimulation during the inspiratory phase alone did cause respiratory acceleration in most instances even under barbitone. In explanation of the results, a theory was presented in which it was suggested that each afferent vagal impulse serves as a unitary contributor to the development of a central state affecting the respiratory centre or its connections. Under urethane a low frequency stimulus or a limited number of impulses at high frequency was considered to result only in a slight build-up of this central state. A rapid and sufficiently prolonged stimulus was considered to result in development of the central state to a greater degree. Comparisons were made with the actions of various drugs in weak and strong concentrations. It was suggested that when the central state was of slight extent or degree, its effect on the respiratory centre was augmentor; when of greater extent or degree, its effect was inhibitor. With barbitone the failure of respiratory acceleration to occur with low frequency stimuli was attributed to the effect of this drug in accentuating the development of an inhibitory level of the central state. The results of the experiments reported upon were interpreted to indicate that whether acceleration or inhibition resulted from different forms of vagal stimulation the type of response was due

to a central selective action to impulses conveyed in a single type of afferent path, rather than to stimulation of specific augmentor and inhibitor types of fibres in the vagi. (Authors' summary.)—*Modification of Respiratory Movements by Vagal Stimulation, H. V. Rice & Margaret S. Joy, Am. J. Physiol., April, 1947, 149: 24.—(G. C. Leiner)*

Breath-Holding Test.—Breath-holding tests were done in 48 aviation students. The conclusion drawn from these experiments is that breath-holding tests cannot be used for prediction of endurance.—*Breath Holding as a Test of Physical Endurance, P. V. Karpovich, Am. J. Physiol., June, 1947, 149: 720.—(G. C. Leiner)*

Immunization against Pneumonia.—The results of immunization against pneumonia for a period of six years with a polyvalent type I and II and, later, type I, II and III pneumococcus polysaccharide are reported; 5,750 persons were immunized and 5,153 kept as controls. During the total period of observation, the number of cases of pneumonia among immunized persons was 99, making the incidence rate 17.2 per thousand. Two hundred and twenty-seven cases of pneumonia occurred within the same period in the control group, which equals an incidence rate of 44 per thousand. The number of deaths due to pneumonia in the immunized group was 40, with a mortality rate of 6.2 per thousand as compared with 98 deaths due to pneumonia (making a death rate of 19.0 per thousand) among the controls. The antigenicity of polysaccharides was tested in mice separately against dilutions of types I, II and III pneumococcus cultures. Protection was found against an average of five hundred thousand lethal doses in 50 per cent of the animals. The blood sera of 400 persons of the immunized group showed an average of a 1,000-fold increase in their protective body titer against type I and a 344-fold increase against type II pneumococcus cultures. The clinical and pathological picture of pneumonia in the two groups (immunized and controls) was generally the same. There were, however,

relatively more bacteremias, toxemias, effusions, empyemata and cases of unresolved and relapsing pneumonia in the controls than in the immunized group. Similarly, there was a difference in the distribution of types in the two groups; more cases of types I, II and III occurred among the controls than among the immunized persons, while the incidence of the higher types was increased in the immunized group as compared with that in the controls. Active immunization in epidemics of pneumonia, in persons in institutions, in elderly persons and in those who have a tendency to recurring pneumonia is suggested. (Author's summary.)—*Pneumonia in Old Age: Active Immunization against Pneumonia with Pneumococcus Polysaccharide; Results of a Six Year Study*, P. Kaufman, with the technical assistance of B. Kaefely, S. K. Kling, C. O'Brien & H. Steine, *Arch. Int. Med.*, May, 1947, 79: 518.—(G. C. Leiner)

Q-Fever.—During the period from February, 1946 through May, 1946, there was an explosive outbreak of Q-fever among the workers in one building of the National Institute of Health. There was a total of 47 cases; data in this paper are based upon 45 of these. American Q-fever is caused by *Rickettsia diaporica* which is immunologically identical with *Rickettsia burneti* isolated in the Australian variety. Diagnosis was based on two criteria: (1) a rise in titer for Q-fever in the complement fixation test during the convalescent phase of the illness; (2) when no sera were obtained during the acute stage, a strongly positive complement fixation reaction during the convalescent stage was considered as diagnostic. Usually, sera were negative until ten to fourteen days after onset of illness. There was no correlation between severity of illness and complement fixation titer. *Rickettsia burneti* were isolated from the blood of 5 cases and from the sputum of one. The incubation period ranged from twelve to twenty-three days. Definite prodromal symptoms, lasting one day, were characteristic; headache, malaise and generalized aching were most common. The severity of the disease varied greatly; several patients

with mild symptoms were able to continue working. There was clinical or roentgen evidence of pneumonitis in 13 patients. Cough occurred in all 13. Five had frankly bloody sputum. Physical signs of pneumonitis were easily detectable in most patients with lung involvement. White blood and differential counts were usually normal. Sedimentation rate was moderately increased. In the pneumonitis cases, chest X-ray films showed either consolidation, as in lobar pneumonia, or findings usually seen in a typical pneumonia of unknown etiology. Convalescence in some cases was prolonged up to three months. Penicillin, sulfadiazine and immune serum exerted no apparent effect on the course of the illness. The authors stress the fact that Q-fever can occur without pneumonitis; lung involvement was present in only 13 of 45 cases in this series.—*Report of an Outbreak of Q-Fever at the National Institute of Health: I. Clinical Features*, C. G. Spicknall, R. J. Huebner, J. A. Finger & W. P. Blocker, *Ann. Int. Med.*, July, 1947, 27: 28.—(H. R. Nayer)

Unusual Pulmonary Disease.—Twenty-six cases of an unusual pulmonary disease occurred at Camp Gruber, Oklahoma, in March, 1944. Every man who became ill had spent some time in an abandoned storm cellar, and none became ill who had not been in the cellar. The onset of the disease was sudden with malaise, fatigue, muscular aching, chill, fever, sweating, constricting pain in the thorax and epistaxis. Clinical signs were scarce. *Monilia albicans* may have been the cause of the disease. The other laboratory findings were of no significance. Chest roentgenograms showed disseminated small areas of infiltration throughout both lungs and enlargement of the hilar lymph nodes. Recovery was slow and incomplete. In February, 1943, 5 patients had been admitted with identical symptoms and signs.—*An Unusual Pulmonary Disease*, J. C. Cain, E. J. Devins & J. E. Downing, *Arch. Int. Med.*, June, 1947, 79: 626.—(G. C. Leiner)

Eruptive Fever.—Twenty cases are reported of a syndrome described in the literature under

the following names: eruptive fever with stomatitis and ophthalmia, *erythema exudativum multiforme* of Hebra, *erythema* or *herpes iris conjunctivae*, *ectodermosis erosiva pluriorificialis* and Stevens-Johnson syndrome. Prodromal symptoms in the respiratory tract are followed by lesions of the skin and mucous membrane of the mucocutaneous junctions, characterized by vesicles and pseudomembranes and accompanied frequently with fever and occasionally with bronchopneumonia. Complete recovery is usual except for rare ocular complications. Ninety per cent of the cases occurred between January and June. The age of the patients was between 18 and 31 years. In 19 cases the onset was with respiratory symptoms. Conjunctivitis developed in 14 cases. All patients had oral involvement. Genital involvement was seen in 13 patients. Bacteriological examination of the various exudates and secretions gave no significant findings. It is probably an air-borne disease due to a virus.—*Eruptive Fever with Involvement of the Respiratory Tract, Conjunctivitis, Stomatitis and Balanitis: An Acute Clinical Entity, Probably of Infectious Origin; Report of Twenty Cases and Review of Literature, S. N. Soll, Arch. Int. Med., May, 1947, 79: 475.*—(G. C. Leiner)

Pulmonary Changes in Glomerulonephritis.—It is claimed that it is possible to establish the diagnosis of glomerulonephritis from the X-ray appearance of the lung only. The distinct features are a dilation of the heart with ingurgitation of the vena azygos which can be seen as a right paratracheal shadow the shape of which may be different in every case but is sufficiently typical to establish the diagnosis. There are two forms of pulmonary congestion of the uremic type: one predominantly passive, hypertensive, chronic, with perivascular and interstitial reaction; the other active, subacute, hypertensive, with interstitial and interalveolar reaction and edematous transudation. The retention of nitrogen plays an important rôle in the production of these changes. However, as there are cases with high nitrogen retention which do not represent the typical lung

picture, there must be other contributing factors. These may be either a toxemic substance which acts upon the endothelial lining of the vessels or an agent which acts on the central vasomotor control directly. The hypertension caused by glomerulonephritis aggravated by anuria or oliguria reacts on the unprepared myocardium and so causes cardiovascular insufficiency. This has been substantiated by electrocardiographic studies. On the other hand, inflammatory nephropathies and chronic sclerosis of the kidney with arterial hypertension and high uremia do not produce any changes in the pulmonary fields. It seems that the circulatory factor plays the foremost rôle in the production of the "azotemic lung." Nitrogen retention itself plays only a secondary rôle by action on the permeability of the membranes or on the vasomotor centre. For this reason, the term "azotemic lung" should be changed to "cardiac lung." Eight case histories are given.—*Aspectos radiológicos del torax en la glomerulo nefritis aguda: Contribucion al estudio del llamado "pulmon azotemico," J. Alvaray C. & E. Zarate, Rev. méd. de Chile, March, 1947, 75: 162.*—(W. Swienty)

Pulmonary Cysts.—Air-filled cysts in the lungs are more common than usually suspected. The writers operated on 6 cases between November, 1943 and September, 1946, and declined to operate on 10 others because of contraindications. Three of the 6 patients were women, one of these a child six years old. These cysts may be congenital or acquired, but it is often difficult to determine their nature. Simple pneumatoceles often disappear spontaneously and as a rule do not require surgery. In diagnosis, simple roentgenograms are the most reliable aid. Visualization of walls and rounded outline helps to differentiate them from tension pneumothorax and empyema. Bronchography is also of assistance and bronchoscopy has both diagnostic and therapeutic value. Thoracoscopy has but limited value and entails some risk. Thoracocentesis and pneumothorax have no place in diagnosis. Surgical indications include severe repeated

hemorrhages, continued purulent sputum, repeated hypertensive pneumothorax with or without empyema and progressive respiratory difficulty. In treatment, drainage with lobectomy, pneumonectomy or segmentary removal of the lung are the measures of choice. Previous determination of the functional capacity of both lungs is most important, as a more extensive, often contralateral, operation than anticipated may be required. In the 6 cases now reported 2 lobectomies, 2 pneumonectomies, one drainage with secondary lobar excision and one removal of a cyst with lobectomy were performed. No postoperative deaths or complications developed. In the 2 pneumonectomy cases, both circulation and respiration improved definitely.—*Tratamiento quirúrgico de los quistes aéreos del pulmón*, O. J. Cames, A. Cesanelli & F. E. Tricerri, *An. de cir. (Argentina)*, March, 1947, 12: 35.—(A. A. Moll)

Postural Therapy in Emphysema.—Patients with respiratory difficulty, either from heart or pulmonary origin, assume, of their own accord, a sitting position for relief. During some research work on abdominal pressure, it was ascertained that patients with marked pulmonary

emphysema benefit when placed in a horizontal position, and even in a modified Trendelenburg position. Twenty patients with considerable emphysema complicating either asthma, bronchitis or tuberculosis of the lung were placed in dorsal decubitus with an 8 to 10 degree Trendelenburg inclination. In some cases this was continuous; in others at intervals; in a few, only at night. In 11, improvement of the condition was immediate; 6 adopted voluntarily the new position for sleeping purposes and 2 even increased the inclination of the bed. Spirometric determinations in 10 patients showed that in a slanting position, as compared to a sitting position, reserve air decreases appreciably. On the other hand, there is but little change in the vital capacity, tidal air, respiratory volume per minute and ventilation equivalent. This treatment must be considered as purely palliative and in the same category as the use of abdominal belts and pneumoperitoneum.—*Acción de la declivoterapia en algunos enfisematosos disneicos*, R. Rimini, J. Duomarco & L. P. Arboleda, *Rev. de tuberc. d. Uruguay*, December, 1946, 14: 231.—(A. A. Moll)

THE EFFECT OF STREPTOMYCIN UPON PULMONARY TUBERCULOSIS

Preliminary Report of a Coöperative Study of 223 Patients by the Army, Navy and Veterans Administration¹

The function of this paper is at once to serve as an introduction for the group of seven papers which follow it and to summarize the results which they will present at length. The introduction is necessary to avoid reiteration of procedural details which were, by agreement, common to the seven studies which the papers will describe. The summary is for the convenience of the more casual reader and includes the judgments of an impartial committee which was appointed to assay the roentgenographic evidence which the studies disclosed.

INTRODUCTION

1. *Background:* Very soon after the discovery of streptomycin in Waksman's laboratory and the demonstration of its effectiveness against the tubercle bacillus *in vitro* (1), Hinshaw and his collaborators undertook to investigate its action in tuberculosis. The results of their experiments upon guinea pigs were published in December, 1944, and their first report of a continuing study (2) upon tuberculosis in man appeared in September, 1945 (3). In January of 1946, the Committee on Chemotherapy and Other Agents of the National Research Council, utilizing funds provided by the Streptomycin Producers Association, launched a small but important study, directed primarily at the toxicity of streptomycin in the clinical treatment of tuberculosis, under McDermott (4).

By May of 1946, sufficient data from these progressing studies were available to the Army, the Navy, and the Veterans Administration to justify an investigation into the effects of streptomycin upon pulmonary tuberculosis in man. Representatives of the three Federal agencies accordingly met to plan the study, with the advice of representatives of the United States Public Health Service, the National Research Council and the National Tuberculosis Association. It was agreed that the venture would be a coöperative one so that a large body of material could be studied, and that each agency would participate to the extent which its supplies of streptomycin, exceedingly small at that time, permitted. It was agreed that a common protocol would be adopted and followed in all cases, so that the evidence which was secured would have more statistical validity. It was agreed that publication of results would be simultaneous and would not be undertaken until four months after the conclusion of treatment.

In consequence of this agreement, the Army undertook to establish a Study Unit at Fitzsimons General Hospital, the Navy at U. S. Naval Hospital, Samp-

¹ Manuscript was prepared by the Streptomycin Committee, Central Office, Veterans Administration (JOHN B. BARNWELL, M.D., PAUL A. BUNN, M.D., ARTHUR M. WALKER, M.D., *Secretary*), at the request of the Surgeons General of the Army, and the Navy, and of the Veterans Administration hospitals which coöperated in the study.

STREPTOMYCIN IN PULMONARY TUBERCULOSIS

son, New York, and the Veterans Administration in its hospitals at Oteen, North Carolina, Sunmount, New York, Rutland Heights, Massachusetts, Hines, Illinois and Livermore, California. Three Study Units were in operation by July, 1946 and each of the seven had at least 15 patients under treatment by November 1946. The terms of the protocol under which the Study Units functioned will be described in the succeeding paragraphs.

2. *Criteria for the Selection of Cases:* Six stipulations were made in this regard:

- (a) *Proved diagnosis:* Tubercle bacilli must have been recently recovered from sputum or gastric contents before treatment was commenced and confirmation of their identity by culture or guinea pig inoculation would have been started.

- (b) *Type of disease:* The presence of exudative lesions was insisted upon and preference was expressed for minimal or moderately advanced disease, although cases of far advanced disease were admissible provided they had an estimated life expectancy of at least one year without streptomycin. The greatest difficulty attached to this criterion. The preference for minimal disease proved to be an error of judgment, based on an insufficient appreciation of the toxicity of streptomycin, and was omitted from later editions of the protocol. The insistence on exudative lesions and the preference for moderately advanced disease proved justifiable but was, in practice, poorly complied with. There proved to be astonishingly few cases to satisfy these criteria, the vast majority having been already subjected to collapse measures and thereby (*vide infra*) been excluded from the study. In consequence, the great majority of cases selected for streptomycin treatment were examples of more extensive disease and contained a more proliferative element—although some exudative component was present in all—than had been originally designed. In a sense this operated as an advantage for the entire gamut of extensive lesions came under observation.

- (c) *Period of observation:* The patients must have been observed for at least sixty days prior to the initiation of treatment in order to establish the trend of the disease. Only patients whose disease was progressive or stationary by roentgenographic and clinical observations, were to be included in the series. It was vital to the significance of the results that the patients not be improving at the time therapy was started. The sixty-day provision was, however, relaxed to permit the treatment of recent "spreads" or pneumonias, once their unfavorable trend was established by successive X-ray films. Despite the importance of this provision and its academic understanding by the participating investigators, a number of cases were included in the series which, in retrospect at least, were judged to have shown improvement in the pre-treatment period. An after-treatment period of 120 days' observation was requested.

- (d) *Activity of patients:* The patients were preferably to have been on complete bed-rest prior to streptomycin therapy but, if this were not the case, the same degree of activity was to be permitted during treatment as had been practiced previous to it. Difficulty was encountered with this stipulation, also. The development of severe vertigo (*vide infra*), for at least a brief period during treatment, enforced more complete rest by many patients than they had pre-

viously observed. It should also be stated that, for administrative reasons, the patients who received streptomycin were assigned to special wards and that, though they received the same diet as other patients, they undoubtedly received more attention from the nursing staff.

(c) *Surgical procedures:* No pneumothorax was to be present on the side towards which treatment was primarily directed, nor was any collapse therapy to be introduced during treatment except in the case of acute contralateral spreads, if the investigator cared to employ it. If contralateral pneumothorax or phrenic paralysis, or if pneumoperitoneum was present prior to treatment, it was to be maintained at its preëxisting level. A preference was indicated against collapse procedures during the after-treatment period of observation, although they were permitted if the investigator deemed them essential to the patient's welfare. This preference and, indeed, the avoidance of surgical measures during treatment were considered necessary in order to determine the incidence and the fate of relapses and spreads.

(f) *Age of patients:* All patients were to be under 45 years of age. This stipulation was made in order to diminish variations amongst the group in this respect.

3. *Regimen:* A daily dosage of 1.8 g. was agreed upon, 0.3 g. being injected intramuscularly every four hours, day and night. A few patients, started late in the study, received a daily dose of 2.0 g., 0.4 g. being injected every four hours from 8 a.m. until midnight. All patients were to receive streptomycin for 120 days. These decisions concerning dosage and duration of treatment were admittedly arbitrary for there were no data on which to base an informed judgment but, in order that the study have any statistical significance, it was considered essential that this first group of patients be treated in accordance with a single regimen.

4. *Laboratory Procedures:* The potential ability of streptomycin to interfere with auditory and vestibular function, renal function and blood formation, having been established by the work of previous investigators (2, 4), the following observations were required: audiogram and caloric test of vestibular function, by a technique which was prescribed, prior to commencing streptomycin therapy and at weekly intervals after the development of vertigo; complete urine analysis on three occasions within two weeks preceding treatment and every two days during treatment; urea clearance and measurement of the nonprotein nitrogen concentration of blood serum immediately prior to treatment and at two-week intervals thereafter; complete blood count prior to treatment and at weekly intervals during therapy. The bromsulphalein test of liver function was to be made at the beginning of treatment and at its end.

In order to observe the progress of disease, the following procedures were also required: stereoscopic and lateral X-ray films of the chest were to be taken immediately before streptomycin administration was commenced, single films being taken every two weeks during treatment, with stereoscopic films every month and films in lateral position as required; a verified sputum or gastric lavage was to be examined for tubercle bacilli immediately prior to treatment

and at two-week intervals thereafter, cultures being made from each specimen; a four-hour chart of temperature, pulse and respiration was to be kept; erythrocytic sedimentation rate, body weight and a detailed physical examination were to be recorded before therapy and at weekly intervals during it; a tuberculin test in serial dilution was to be made, and a photograph in the nude taken, prior to therapy and at its conclusion.

In addition to these procedures, the Study Units were asked to make periodic measurements of the streptomycin concentration of blood serum, collecting the blood for this purpose at recorded times after the injection of streptomycin. All positive cultures of tubercle bacilli obtained immediately before, during, and after treatment were to be frozen and the sensitivity of the organisms to streptomycin was to be determined as the laboratories developed the techniques to accomplish this. The liquid media to be employed in this determination were not prescribed, the laboratories being at liberty to choose that used by Youmans (5) or Dubos (6).

The rather formidable battery of procedures which has been described imposed a heavy burden upon the laboratories concerned and sensibly limited the number of patients who could be treated with streptomycin. As time went on, it was found that the interval between many of the procedures could be safely lengthened. None of them could be abandoned if the welfare of the patient was to be safeguarded and the necessary information be garnered.

5. *Liaison*: After preparation of the protocol which has just been described, and its acceptance by the seven Study Units, the Joint Streptomycin Committee of the three Federal agencies attempted to maintain, between the Units, the liaison which was so essential to any rapid progress of the investigation. With the design of attaining uniformity of case material, one of its members visited all the Units to assist in the selection of cases. Thereafter, visits were made periodically and the investigators were kept informed of one another's progress by the circulation of monthly reports. The investigators met with the Joint Committee and with a group of consultants in December, 1946, in January, 1947, and again in May of 1947, to view X-ray films, exchange reports and make plans for the future of the study.

6. *Controls*: It was the original decision of the Committee to have the Units select suitable cases and then divide them at random into two groups, the one to be treated with streptomycin, the other to provide controls. It seemed a feasible procedure at the time. The very scanty supplies of streptomycin, and the real ignorance of its effectiveness, made it reasonable to leave half the patients without treatment or, rather, to treat them by other methods than streptomycin. Some, at least, of these methods would have left the pulmonary lesions available for observation and, thus, for comparison with those in patients receiving streptomycin. In retrospect, it would have been highly desirable to do this, for, admitting the difficulty of matching cases and the unpredictability of the disease, the results of streptomycin therapy in pulmonary tuberculosis have proved to be so much less definite than in certain other tuberculous lesions (7) that the existence of a control group would have facilitated their evaluation. The Committee's decision had, however, been made *in racuo*. When the clinical material

in the several hospitals was examined, there was, as has been said, the greatest difficulty in finding cases to satisfy the criteria which the Committee established. To divide this material in two groups would, it was felt, reduce the number receiving streptomycin so far as to affect the statistical significance of the results. The purpose of controls, in such a situation as this, is to compare the results of one form of therapy with those of another. In so far as a comparison with the effects of bed-rest upon pulmonary tuberculosis is concerned, these cases may reasonably be said to serve as their own controls. According to the terms of the protocol, they had been observed on bed-rest for at least sixty days and, with that treatment, their pulmonary lesions had either progressed or remained stationary. Any improvement which occurred, following the institution of streptomycin therapy, could therefore be attributed to its effect. The more striking and uniform the improvement, the more rational would be the attribution. The study, as it was performed, provides no basis for a comparison between streptomycin and any collapse procedure.

RESULTS

1. *Clinical Material*: A total of 223 cases of pulmonary tuberculosis have been treated with streptomycin by seven Study Units under the terms of the protocol which has just been described. Following the completion of treatment, 195 of these patients have now been observed for an average of 117 days. In one Unit it became impossible, for administrative reasons, to maintain observation for more than thirty days; if this hospital be excluded, the average period of observation for the group was 138 days, varying from ninety-nine to 176 days in the several Units.

TABLE 1
Clinical material—treated cases reported by investigators

Number..... Per cent.....	PA- TIENTS	SEX		RACE			AGE			STAGE OF DISEASE		
		M.	F.	W.	NW.*	Other	18-30	31-45	46-50	F.A.	Mod.	Min.
223	219	4		167	53	3	161	56	6	156	65	2
100	98.2	1.8		74.8	23.8	1.4	72.2	25.1	2.7	70.0	29.1	0.9

* Non-white.

As a glance at table 1 will disclose, the series consisted predominantly of white males, less than 30 years of age, with far advanced tuberculosis. There was a sufficient number of colored patients (24 per cent) to permit separate evaluation of this racial group. In other respects the series was quite homogeneous. It included only 2 Orientals and one American Indian, 4 females, 6 persons over 45 years of age, and 2 patients with minimal tuberculosis. The results have been sufficiently uniform so that some conclusions appear warranted, in so far as the immediate and mediate effects of this particular regimen (1.8 g. a day for 120 days) are concerned. They will be described under the headings of roentgenographic, clinical and laboratory observations:

2. *Roentgenographic Observations:* Since the lesion under discussion is a pulmonary one, the most important single observation to be made would appear to be the roentgenographic changes which occur during the course of treatment. It is unfortunate, therefore, that this observation must have such a large subjective element, and be so literally in the eyes of the beholder that its validity has been suspect. In an attempt to minimize this objection, the President of the American Trudeau Society, at the request of the Veterans Administration, appointed a jury of nine phthisiologists, no one of whom had been concerned with the investigation other than as a matter of general interest. The following seven members of this jury met and read X-ray films for six consecutive days in July, 1947: Drs. Bruce H. Douglas, H. Harold Fellows, Kirby S. Howlett, Jr., N. Stanley Lincoln, H. McLeod Riggins, Rollin D. Thompson and Julius L. Wilson.

Among the 387 cases which were presented to the jury at that rather rigorous session, there were 219 from six of the seven Units contributing to this symposium. One hundred and thirty-one of these 219 had been treated with streptomycin, 88 had not been so treated. Films from the seventh Unit (Fitzsimons) were unfortunately not available, but in the opinion of a previous jury, working under less favorable circumstances to be sure, the results from this Unit had been superior to a majority of the others. The omission is not, therefore, believed to have weighted the evidence in favor of streptomycin; rather the reverse.

The details of the presentation were arranged with the advice of statisticians and with the design of removing the influence of external suggestions and, indeed, of the viewer's own memory. Each juror had his own set of three viewing boxes, removed in space though in the same room, and no consultation between jurors took place. Films from treated and untreated cases were mixed at random and were unmarked with the exception of a few films from a single Unit which had been crayoned in a suggestive manner. The envelopes containing the films were similarly unmarked or their markings concealed. Each case was viewed by three jurors. Although each case was reviewed, as will appear, from several points of view, no juror saw films from the same case more than once in the same day. Each juror recorded his answer to the several questions which were asked of him on specially prepared cards at the time he viewed the case and did not, subsequently, see these cards. It was, in short, a sincere attempt to obtain completely unbiased judgments from the jury; an attempt that was, perhaps, unnecessarily elaborate considering the vast number of films which were examined.

Each case was represented by three films which were viewed, either individually or in a variety of groupings, on successive days. In the cases which had received streptomycin, these films had been made, respectively, sixty days prior to the commencement of therapy, on the day upon which it was started, and at the conclusion of treatment. In the untreated cases, the films were similarly spaced in time. A vast amount of statistical analysis upon the 5,000 cards which resulted from this review will have to be made. But the following data have been selected from them upon the points which seem most germane to the present review:

Type of lesion: On the second day of the session, the jurors were asked to

describe the type of pulmonary lesion in terms, amongst others, of extent, character and stability. They were to do this by examining a single film, the one taken immediately before the commencement of streptomycin or, in the untreated cases, the film (#2) which corresponded to it in time. Table 2 indicates the results of this estimate.

Of the 131 cases about to receive streptomycin, 108 (83 per cent) were regarded as far advanced, with the balance moderately advanced. This classification

TABLE 2
Röntgenographic description of lesions by jury

HOSPITAL	STAGE OF DISEASE			EXUDATIVE COMPONENT				STABILITY	
	FA	MOD	MIN	100%	75%	50%	25%	STABLE	UN-STABLE
Treated Cases (131)									
Oteen.....	9	6	0	2	7	5	1	0	15
Sunmount.....	24	4	0	6	16	6	0	6	22
Rutland Heights.....	16	1	0	4	8	4	1	2	15
Hines.....	15	4	0	1	11	7	0	4	15
Livermore.....	15	5	0	3	7	9	1	2	18
Sampson.....	29	3	0	4	14	12	2	5	27
Total {									
Number.....	108	23	0	20	63	43	5	19	112
Per cent.....	82.5	17.5	0	15.3	48.1	32.8	3.8	14.5	85.5
Untreated Cases (88)									
Oteen.....	0	3	8	0	1	3	7	4	7
Sunmount.....	2	13	3	0	4	12	2	3	15
Rutland Heights.....	10	5	2	2	8	7	0	1	16
Hines.....	8	9	3	0	4	9	7	7	13
Livermore.....	6	14	2	0	6	10	6	2	20
Total {									
Number.....	26	44	18	2	23	41	22	17	71
Per cent.....	29.5	50.0	20.5	2.2	26.1	46.6	25.0	19.3	80.7

agrees reasonably well with that of the investigators who, grading the entire series of 223 cases (table 1), recorded 70 per cent as far and 29 as moderately advanced. One hundred and twenty-six (96 per cent) of the 131 cases were said by the jury to have an exudative component of 50 per cent or more in at least one lung, and only 5 cases were considered to be predominantly proliferative disease; 86 per cent of the lesions were termed unstable. The 88 cases which did not receive streptomycin were examples of less advanced disease (21 per cent being graded as minimal) with a higher percentage of proliferative component (it being predominant in 25 per cent), though the instability of the lesions was regarded as quite similar in the two groups (81 and 86 per cent).² Bilateral

² The jury had an opportunity of recording four gradations of the exudative component, but was required to divide the cases into only two categories of stable or unstable. This may explain the jury's finding a marked difference in the exudative component of the treated and untreated lesions but no difference in their stability.

lesions were present in 59 per cent of the treated, and in 62 per cent of the untreated cases.

In referring to the patients who did *not* receive streptomycin as "untreated cases," the use of the word "controls" has been purposely avoided. The primary purpose in presenting them to the jury was to rid the jurors' minds of bias concerning any individual case and, though they were informed that both treated and untreated cases were to be viewed, they were given no information as to the proportion in which the two groups were to be mingled. The untreated cases were, for the most part, selected by the Study Units at random, without reference to the type of disease or its outcome, the only criteria being that they should have X-ray films properly spaced in time and have been treated by bed-rest alone without collapse procedures. They were all proved cases of pulmonary tuberculosis and though, as has been pointed out, they contained somewhat less advanced and more productive lesions, they may be regarded as analogous types of disease and, in that sense, as a control series.

Status of disease at beginning of "treatment": On the third day of the session, the jurors viewed simultaneously the film taken sixty days prior to treatment and that taken immediately before its commencement; or, in the untreated cases, the films corresponding to these (that is, films 1 and 2). The results of this procedure appear in table 3 I. In this review each lung was judged separately, so that there were 222 lesions in the cases to be treated and 142 in those untreated. In the opinion of the jurors 64 (29 per cent) of the lesions which were to be exposed to streptomycin had become either smaller or harder (that is, had improved) during the pre-treatment observation period and 132 (59 per cent) had either remained stationary or had progressed. Although nearly one-third of the lesions were thus regarded as having improved prior to streptomycin therapy, this does not indicate as frequent violation of the terms of the protocol as the statement suggests; simultaneous progression of a lesion in the contralateral lung had often occurred, and it was against this lesion that treatment was to be directed. Of the cases which were not to receive streptomycin, a somewhat higher percentage (36 per cent) of lesions were judged to have improved in the interval, a difference which would militate against streptomycin during the subsequent treatment period in a comparison between the two groups.

During this same step in the analysis, and from viewing the same two films, the jurors were asked to predict whether "in their experience and in view of the observed changes, they would expect significant improvement to occur within the next four months with continuation of the same regimen." To this question (table 3 II), in the cases selected for streptomycin therapy, the jurors replied "never" or "rarely" in 128 (58 per cent), "occasionally" in an additional 46 (21 per cent) and "often" in but 17 (8 per cent). About the untreated cases, the jurors were more optimistic, using the adjectives "never" or "rarely" in only one-third (33 per cent) and "often" in 29 (20 per cent).

Changes occurring during "treatment": On the fourth day of the session, each of three jurors viewed all three films of each case simultaneously, the two lungs being again marked separately, and described the changes which had occurred

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in the exudative lesions during 120 days of treatment; or, in the untreated cases, changes between the films similarly spaced in time (that it, between films 2 and 3). The results of this examination appear in table 3 III.

Of the lesions, 189 (85 per cent) were judged to have improved during streptomycin therapy (that is, to have "disappeared," or become "smaller" or "harder"), 21 (10 per cent) to have remained "unchanged" and but one to have become "larger." In the untreated series, less than one-third (30 per cent) were said to have improved, 78 (55 per cent) to have remained unchanged, and 6 (4 per cent) to have become worse.

Agreement between jurors: The validity of the above data would gain weight in proportion to the unanimity with which the jurors agreed upon them. In compiling sections I and III of table 3, lesions upon which at least two of the three jurors did not agree were placed under the column headed with a question mark.

TABLE 4
Agreement between jurors on changes during treatment (according to table 3 III)

TREATED CASES	ALL 3 AGREE	ALL 3 AGREE IF B AND C* ARE EQUAL	NUMBER OF LESIONS
Oteen.....	15	1	28
Sunmount.....	33	6	45
Rutland Heights.....	18	5	32
Hines.....	20	2	34
Livermore.....	20	4	32
Sampson.....	26	6	51
Total {Number.....	132	24	156 of 222
Per cent.....	59.5	10.8	70.3 of 100

* B = Smaller.
C = Harder.

There were 26 of these disagreements (12 per cent) in section I and 11 (5 per cent) in section III; or to put a pleasanter construction upon it, there was agreement, of this order, in 88 and 95 per cent of the two sections. To further analyze this point, section III, the most important of the group to the present issue, was further examined. The results appear in table 4. All three jurors agreed in their description of the lesion's course in 132 instances (60 per cent) and if, as seems fair, "smaller" and "harder" are accepted as synonymous, agreement was unanimous on an additional 24 lesions (10 per cent), or on a total of 70 per cent.

Date at which greatest improvement occurred in patients treated with streptomycin: In considering future modifications of the 1.S g.-120 day regimen employed in the present study, it seemed important to determine the time, during streptomycin therapy, at which maximum improvement occurred. With this in mind the jury, sitting as a whole on this occasion, was asked to view the X-ray films, taken serially at monthly intervals prior to and during therapy, of a group of patients. Lesions in 44 lungs were examined from this point of view. It was voted that

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maximum improvement was present on the sixtieth day of therapy in 25 instances and in 8 of the remaining 19 (a total of 75 per cent) on the ninetieth day film. A more gradual improvement might or might not continue thereafter. The reverse of this question, the date at which, after initial improvement, progressions of the lesions occurred during therapy, was similarly reviewed. Of 15 lungs examined with this point in mind, it was agreed that 8 did not become worse until after the sixtieth day and 7 until after the ninetieth-day film.

Cavitation: An attempt was made to obtain the jurors' opinion of the fate of pulmonary cavities during streptomycin therapy. The difficulty of distinguishing between various types of cavities and of recording the changes in multiple cavities made this attempt unsuccessful. The jurors were impressed by observing thinning of cavity walls but, beyond that, there emerged only the very general conclusion that the changes were variable. In the opinion of the investigators (table 5), of 182 cavities present at the beginning of treatment, 47 (26 per cent) were either closed or lost to view at the end of treatment and an additional 67 (37 per cent) became smaller. The remaining 68 cavities (37 per cent) were either unchanged or became larger.

Extension of disease during streptomycin treatment: According to the jury only one (0.5 per cent) of the patients receiving streptomycin had more extensive disease at the end of therapy than at its beginning (table 3 III). Since, except in a few selected cases, the jury did not view films taken during therapy, they were merely in a position to describe the overall effect, and necessarily missed the instances in which exudative lesions became worse during the latter half of treatment but not sufficiently so to outweigh an initial improvement. According to the investigators (table 5) relapses of this sort occurred in 18 instances (8 per cent) of 216 patients.

Roentgenographic changes after streptomycin treatment: On this point the jury had no opportunity of forming an opinion, since they were shown no after-treatment films. One hundred and ninety-five patients have been observed for an average of 117 after-treatment days by the investigators (table 5): 77 (40 per cent) showed continuing roentgenographic improvement, 86 (44 per cent) progressed neither in one direction nor the other, and the remaining 32 patients (16 per cent) had either extensions or spreads of their pulmonary disease. The majority of these relapses occurred within the first thirty days after treatment was stopped.

Summary of roentgenographic observations: The roentgenographic evidence in 131 of 221 cases of pulmonary tuberculosis treated with streptomycin (1.8 g. daily for 120 days), at seven hospitals cooperating in this study, was reviewed by a jury of seven phthisiologists appointed by the American Trudeau Society. The X-ray films of 88 untreated cases were similarly examined. Films from the two groups were not distinguishable from each other by any markings and were viewed in random sequence. The treated cases were, on the whole, examples of more advanced disease and had a larger exudative component than those who were not treated, but the instability of the lesions and the incidence of bilateral lesions were of the same order in both groups.

It was the judgment of the jury that little or no improvement occurred in the proliferative or fibrocavernous lesions of the treated patients. In this respect the treated and untreated groups were similar. In the case of exudative lesions treated by streptomycin, however, 85 per cent of the lesions cleared somewhat during treatment and, with a single exception, the balance remained stationary. This result was observed although two-thirds of the lesions had been recorded as stationary or progressive at the time treatment was instituted and although the jury, on the basis of its examination of pre-treatment films, had predicted that 58 per cent of them would never or rarely improve on bed-rest alone in a similar period of time. In the untreated cases, the adjudged results were very different; only 30 per cent of the exudative lesions improved on bed-rest during the 120-day period, although 36 per cent had improved in the period of preliminary observation. This incidence of improvement (30 per cent) tallied reasonably well with the prediction (20 per cent) of the jury, made after its examination of the earlier films, of what would often occur.

No claim is made that the untreated cases represent ideal controls. Indeed, for the purposes of argument, they may be disregarded as controls and the contrast in results between the two groups may be ignored. The conclusion remains the same. The case for streptomycin rests primarily on the fact that, during treatment, some degree of roentgenographic clearing occurred in 85 per cent of lesions of which a majority had been stable or progressive before streptomycin was instituted. This appears adequate evidence of the superiority of streptomycin and bed-rest to bed-rest alone. As to the effects of streptomycin without bed-rest, no evidence had been adduced nor is it planned to obtain any. Streptomycin must be regarded as ancillary to bed-rest and not as a substitute for it.

There is no intention of exaggerating the extent of the clearing which, it appears, the use of streptomycin produced. Only 3 of 222 lesions entirely disappeared during therapy (table 3 III). In a very considerable number, the clearing was minimal. The fact remains that streptomycin altered the trend of the disease. In the instances where this new and favorable trend is not marked nor continued, it may still be sufficient to make the patient eligible for a thoracoplasty which he could not, before, have endured. The comment of one Study Unit (Sampson), that thoracoplasties had been made possible in 10 of a series of 24 patients with large cavities, may prove a very proper indication of the usefulness of streptomycin.

A final comment derives from the observation (table 5) that 8 per cent of patients showed extension of infection during the last two months of therapy and 16 per cent showed extension of infection soon after its conclusion. In the former instance certainly, and in the latter instance probably, the action of streptomycin has been suppressive rather than curative. This observation must be borne in mind in determining the duration of streptomycin therapy and in considering the desirability and timing of surgical measures.

In this section of the paper, dealing with roentgenographic changes, the observations and opinions of the jury have been stressed almost to the exclusion

of those of the investigators. This has been deliberate and with the design of excluding any bias which might, theoretically, influence the latter group in recording observations that have a considerable subjective element. It was this rationale which was behind the decision to use a jury. The judgment of the investigators is, however, distinctly important for the purpose of this summary article. It was formed with more deliberation; it was based on access to more films; it is available on 223, rather than on 131 patients. It is recorded in table 5.

TABLE 5
Roentgenographic changes, according to investigators—treated cases

	NUMBER	PER CENT
During Pre-treatment Observation (223 cases)		
Progression.....	168	75.3
Stationary.....	38	17.1
Regression.....	17	7.6
During Treatment—exudative lesions (216 cases)		
Progression.....	1	0.5
Progression after regression.....	18	8.3
Stationary.....	14	6.5
Slight regression.....	54	25.0
Considerable regression.....	123	56.9
Complete regression.....	6	2.8
During Treatment—cavities (182)		
Larger or unchanged.....	68	37.4
Smaller.....	67	36.8
Closed or lost to view.....	47	25.8
During Post-treatment Observation (195 cases)		
Progression.....	32	16.4
Stationary.....	86	44.1
Regression.....	77	39.5

In the opinion of the investigators, at the time treatment with streptomycin was started, the disease was progressive or stationary in 92 per cent of the patients. In the opinion of the jury (*vide supra*), only 67 per cent of the lesions fell in these categories. One reason for this discrepancy, other than a conflict in judgment and the quantitative difference in material, has already been pointed out and undoubtedly accounts for a portion of it. A patient with a progressing lesion in one lung, against which treatment was to be directed, would be recorded by the investigator as progressive even though he might have a regressing lesion in the contralateral lung. By the jury, both the progressing and the regressing lesions would be recorded since they were asked to judge each lung separately.

There happens to be precise agreement between the investigators and jury upon the roentgenographic changes which occurred in exudative lesions during

streptomycin therapy. According to the investigators, some degree of clearing occurred in 85 per cent of patients. According to the jury, 85 per cent of lesions showed changes of this character.

3. *Clinical Observations:* While it is a little difficult to present statistics on "increased morale" and "increased sense of well-being," definite as they may be and constantly as they are referred to by the investigators, the majority of the clinical observations are objectively made and can be readily measured. Results of the investigators' observations upon weight, appetite, cough, sputum and fever appear in table 6.

Summary of clinical observations: As a glance at table 6 reveals, there was a markedly favorable effect upon body weight, appetite, cough and sputum in approximately 80 per cent of the 223 patients. A sensible reduction of temperature in those who were febrile occurred in nearly as high a percentage. With

TABLE 6
Clinical observations during therapy

OBSERVATION (223 PATIENTS)	INCIDENCE		EXTENT
	Number	Per cent	
Weight increase.....	188	84.3	12.3 lbs. (avg.)
Appetite increase.....	198	85.2	Marked
Cough decrease.....	178	79.8	Marked
Sputum decrease.....	178	79.8	80 to 31 cc. ¹
Temperature decrease.....	117	73.1 ²	To normal in 76 patients
Sedimentation rate decrease.....	94	51.1 ³	Definite

¹ Average daily output, before and after treatment, of 115 patients from four Units reporting on this point. Two other Units report amounts became "negligible."

² Of the 160 patients who were febrile at commencement of therapy.

³ Of the 184 patients who had increased rates at the commencement of therapy.

the exception of weight, all of these effects were prompt in making their appearance, and were usually fully developed within the first two to four weeks of therapy. The increase in weight appeared more slowly and was, at times, a gradual rise continuing throughout treatment and into the subsequent observation period (Rutland). Sputum was reduced in viscosity and purulence as well as volume. These striking reductions in the signs and symptoms of toxemia were usually associated with concomitant improvement in pulmonary lesions but occasionally occurred, to some degree, in the absence of such improvement.

4. *Laboratory Observations:* The development of resistance to streptomycin by tubercle bacilli will be dealt with in section 5 of this paper. The other laboratory observations are, for the most part, concerned with discovering the toxicity of streptomycin. Those which are not so concerned will be summarized first.

Sedimentation rate of erythrocytes: One hundred and eighty-four (83 per cent) of the patients in this series had elevated sedimentation rates at the time

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streptomycin treatment was started, a slightly higher percentage than were febrile. In 94 (51 per cent) of these patients (table 6), a definite reduction of the rate occurred during therapy though the extent of this reduction, like that of the original increase, was variable and infrequently returned it to normal. One Unit (Sunmount) comments that the reduction was most marked in patients whose pulmonary cavities closed during therapy.

Sputum conversion: All investigators comment on the increasing difficulty with which tubercle bacilli could be found in sputum during therapy, but, in the matter of actual conversion, our data are not sufficiently precise. Apparently there were 82 conversions from positive to negative during treatment (43 per cent) in the 190 cases which have been reported upon in this connection. Apparently 69 of these were found negative by culture and 13 by smear only. But neither the methods nor the criteria employed are entirely clear in the investigators' reports. Nor, indeed, is it clear that, in this particular situation, cultures are preferable to smears. Two Units (Hines and Rutland) comment on the fact that cultures became negative more frequently than smears, a situation which suggests the presence, in smears, of organisms which are either nonviable or incapable of reproduction and growth.

Concentration of streptomycin in blood serum: Periodic determination of streptomycin concentrations were made throughout therapy at varying intervals following intramuscular injections. Although there were considerable variations from individual to individual, the averages from the several Units agreed well. The average serum concentration one hour following intramuscular injection (88 patients) was 17.5 mcg. per cc. and four hours following injection (63 patients) it was 11.9 mcg. per cc. One Unit (Livermore) obtained results at variance with these, consistently recording a two-hour concentration of the order of 40 mcg. per cc. It was at first suspected that this might reflect some nephrotoxic effect of streptomycin but this would not appear to have been the case and its explanation is not clear.

Tuberculin reaction: All but one of the 223 patients were positive to the tuberculin test (Mantoux) prior to therapy and all who were tested (144) were similarly reactive 120 days later. Data on the quantitative aspects of the reactions are not available.

Toxicity: The remaining paragraphs of this section deal with the toxicity of streptomycin, of which the manifestations and incidence are listed in table 7. At the time the study was undertaken, it was already understood, from the work of previous investigators (2, 4), that interference with eighth cranial nerve and renal function were the important disabilities most likely to be encountered. This understanding proved correct although, as the study progressed, the importance of the former appreciated while that of the latter depreciated. Omitting, for the moment, mention of vestibular dysfunction, streptomycin proved relatively nontoxic in comparison with any potent drug other than penicillin. There were no deaths attributable to it. In only 8 patients (4 per cent) did treatment have to be stopped because of toxemic signs and in only 9 (4 per cent) did it have to be interrupted.

One complication of therapy, which is described only in the papers from Fitz-

simons and Livermore, although it was encountered by all Units, involved the medical staff rather than the patients. Nurses and pharmacists who handled streptomycin solutions frequently developed a sensitivity to the drug which manifested itself by an erythematous skin or mucous membrane reaction involving chiefly the hands but occasionally, by misadventure, affecting the face or conjunctiva.

Minor reactions or reactions which may be fortuitously related to streptomycin therapy: Pain at the site of intramuscular injection was constantly observed but was scarcely greater than that encountered with the administration of penicillin. Circumoral paresthesia was common. Slight and transient elevations of temperatures occurred early in the course of therapy in 19 instances (9 per cent). All but

TABLE 7
Toxic manifestations accompanying therapy

MANIFESTATIONS	INCIDENCE IN 223 PATIENTS	
	Number	Per cent
Sufficiently severe to stop therapy.....	8	3.6
Sufficiently severe to interrupt therapy.....	9	4.0
Fever, slight.....	19	8.5
Nausea, vomiting.....	22	10.0
Eosinophilia (5 to 50 per cent).....	155	69.5
Dermatitis, mild.....	41	18.4
Dermatitis, exfoliative.....	3	1.4
Urinary casts.....	150	67.3
Urinary albumin.....	45	20.2
Urea clearance, Decrease of.....	1	0.4
Vertigo.....	204	91.5
Caloric stimulation, Diminished response to.....	111	77.1 ¹
Tinnitus.....	74	46.8 ²
Hearing, Diminution of.....	1	0.4

¹ Of 144 patients upon whom this test was made.

² Of 158 patients reported upon in this regard.

5 of these reactions were reported from a single Unit and it may be that, in the other Units, they were masked or differently regarded. Nausea and vomiting, occasionally of sufficient severity to warrant the interruption of treatment, occurred in 22 cases (10 per cent). One Unit (Livermore) reported the rather constant development of a euphoria in their patients. Neither psychosis nor jaundice was commented on by the present investigators, though several cases of the former and one of the latter have been reported in the larger study (7) of which this forms a part. The causative connection of streptomycin therapy with them is putative. The histamine-like reactions encountered previous to the spring of 1946 did not appear in this investigation and may, therefore, be attributed to impurities present in the preparations in use at that time.

Blood dyscrasias: No instances of blood dyscrasia appeared in the present series but it is felt that the subject should be mentioned. Two cases of aplastic

anemia, at least one of which terminated fatally, occurred during streptomycin treatment of extrapulmonary tuberculosis at one Unit (Fitzsimons). Although the investigators hesitated to attribute the dyscrasia to streptomycin, it does not seem unreasonable to do so in view of the fact that 5 cases (0.7 per cent) of relatively mild leucopenia with neutropenia and one case of agranulocytosis (in a patient with miliary tuberculosis) appeared in a series of 800 cases treated with streptomycin (7). The reactions were quite definitely due to the drug in the sense that they were alleviated by its withdrawal.

Sensitivity reaction: An eosinophilia, exceeding 5 per cent and reaching as high as 50 per cent, was observed in 155 patients (70 per cent). It was usually below 15 per cent. It appeared early in the course of treatment and often persisted intermittently until treatment was stopped. A pruritic, erythematous maculopapular skin eruption appeared after about ten days of treatment in 41 patients (18 per cent). The pruritus was usually easily controlled by benadryl and the eruption disappeared with continued treatment. In 3 instances, however, a severe exfoliative dermatitis developed and in only one of these could therapy be resumed subsequently.

Renal damage: Casts, although absent from the urine in pre-treatment specimens, were noted in the urine of 150 patients (67 per cent) at intervals throughout streptomycin therapy. Albuminuria was a less constant finding (20 per cent). No special attempt was made to maintain an alkaline reaction in the urine. The incidence of cylindruria varied enormously amongst the several Units due, it may be, to the care with which it was searched for and reported. The appearance of casts is probably, therefore, an even more constant concomitant of streptomycin therapy than the above figure would lead one to believe. Although these findings strongly suggest that streptomycin is a nephrotoxic drug, the damage in this series, with a single exception, was not sufficiently serious to be reflected by changes in urea clearance or in the concentration of nonprotein nitrogen in the blood serum. Nor, in the experience of the single investigator who mentions this point (Sunmount), was there any delayed damage as estimated by decreases of urea clearance over an after-treatment observation period of six months. The single case, to which allusion was made, had a definitely decreased renal function at the time streptomycin was instituted and, on that account, had very much higher serum streptomycin concentrations than his routine dosage would ordinarily impose. His urea clearance decreased from 41 to 10 per cent of normal and the nonprotein nitrogen concentration of blood serum increased to 63 mg. per 100 cc. before treatment was stopped. In this case, the renal damage inflicted by streptomycin would appear to be permanent, for renal function is still below the pre-treatment level a year after therapy was stopped. The results of the present series may underestimate the nephrotoxic action of streptomycin for, in the larger study (7) of which it is a part, sufficient interference with renal function occurred in 17 instances (2.3 per cent) to require cessation of therapy.

Eighth nerve damage: Some degree of vertigo appeared in 204 of the 223 patients (92 per cent) and was accompanied by ataxia. It varied in degree from a

slight and occasional sensation of light-headedness to a severity which incapacitated the patient for all movements. Its time of onset also varied widely. It occurred as early as the seventh and as late as the ninety-ninth day but made its first appearance during the fourth or fifth week of therapy in a vast majority of the patients. After persisting in decreasing degree for about one month, the subjective vertigo almost always disappeared and, as the patient learned to use his other senses, he became able to accommodate, at least partially, for the ataxia. The vertigo was more severe and the accommodation was less complete amongst the older patients. Some degree of disability persisted even during after-treatment observation, in the sense that many of the patients were unable to walk heel-to-toe in a straight line and experienced some difficulty in focusing their vision, particularly after turning their heads sharply. Definite objective evidence of this interference with vestibular function was provided by the diminution or absence of response to caloric stimulation which was exhibited by 111 of the 144 patients (77 per cent) upon whom this test was reported. The time of onset of this diminished response is similar to that of the subjective symptoms of vestibular disturbance but, unlike them, it has shown no tendency to improve during the remainder of treatment or during the subsequent period of observation. It may prove to be permanent. The discrepancy in incidence between vertigo (92 per cent) and labyrinthine dysfunction as revealed by the caloric test (77 per cent) is difficult to understand.

The frequency with which tinnitus was reported varied widely in the different Units. It occurred in approximately one-half of the patients.

Audiometric readings disclosed a loss of hearing, sometimes in the low and sometimes in the high range, in 5 cases (2 per cent), but these changes were slight and temporary, disappearing with continuation of treatment. There was only one instance of deafness, in the sense of a diminished ability to hear the spoken voice. This occurred (Rutland) in a patient who developed an extremely severe exfoliative dermatitis. Unlike the vestibular disturbance, the deafness is reversible. In this instance, and in 9 instances (1.2 per cent) in the larger series to which reference has been made (7), it returned towards or to normal within one month after therapy was discontinued.

Liver function: As revealed by the bromsulphalein test, streptomycin had no hepatotoxic action in the 55 patients upon whom this observation was reported.

5. *The Development of an in vitro Resistance to Streptomycin by Tubercle Bacilli:* The data which the Army, Navy, Sunmount and Livermore Units have accumulated on this point are summarized in table 8. The other Units have, thus far, been unable to obtain these data on their patients. For the purposes of this discussion, organisms which are only resistant to less than 10 mcg. per cc. will be regarded as sensitive to streptomycin, since concentrations of that order, or higher, are maintained in the blood on the regimen of this study.

It will be observed (table 8) that 95 per cent of the strains of tubercle bacilli isolated from patients who had *not* received streptomycin were sensitive to it. The growth of all these strains was inhibited by culture media containing less than 3 mcg. per cc. and the vast majority of them by less than 0.5 mcg. per cc.

In bacilli isolated from patients who had received streptomycin, the development of *in vitro* resistance was noted as early as the thirtieth day of treatment. After sixty to ninety days of treatment, only 36 per cent of the strains were sensitive, and 44 per cent were resistant to more than 100 mcg. per cc. After 120 days, only 22 per cent were sensitive and 65 per cent were resistant to more than 100 mcg. per cc.

Within ninety days, then, and to an even greater extent within 120 days, a great majority of the isolated strains subjected to this test had become resistant *in vitro* to concentrations of streptomycin which were far beyond those which could be obtained in the blood-stream by any plausible regimen. Once developed, the resistance, with but 2 exceptions (Livermore), has shown no tendency to diminish during after-treatment observation periods covering as long as ten months (Fitzsimons).

TABLE 8
Development of resistance to streptomycin by tubercle bacilli *in vitro* during treatment

TIME	NUMBER TESTED	RESISTANT, IN MCG. PER CC., TO							
		10		10-99		100-499		500	
		Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Pre-treatment ¹	194	184	94.8	10	5.2	0	0.0	0	0.0
60-90 days.....	39	14	35.9	8	20.5	3	7.7	14	35.9
120 days.....	88	19	21.7	12	13.6	9	10.2	48	54.5

¹ This group includes (Fitzsimons) a number of tuberculous patients who did not receive streptomycin subsequently.

Summary of laboratory observations and resistance: The examination of sputa for tubercle bacilli revealed an increasing number of negative specimens during the course of streptomycin therapy. The data do not permit a definite statement as to the incidence of true conversions. Apparently it was of the order of 40 per cent. The permanence of these conversions may properly be suspect and, indeed, it is less than clear in several of the papers upon how many observations they were based. Even accepting the above approximation, however, its low degree, in comparison with the much higher incidence of roentgenographic and clinical improvement, constitutes additional evidence of the suppressive rather than the curative action of streptomycin. The measurement of erythrocytic sedimentation rates added little to the evidence gained from other clinical data. The measurement of streptomycin blood concentrations revealed them as ranging, on the average, from 20 to 10 mcg. per cc. in the four-hour interval between injections. Once this fact was established, the measurement seemed only useful in the presence or detection of renal insufficiency. The remainder of the laboratory measures were designed, and were used, to

discover the presence and incidence of toxemic manifestations. With the outstanding exception of vestibular dysfunction, these manifestations were sufficiently unimportant (for example, eosinophilia, fever) or sufficiently rare (for example, exfoliative dermatitis, definite renal damage) to make the investigators conclude that streptomycin was relatively nontoxic, for a potent drug used over such protracted periods of time and in such considerable dosage. The interference with vestibular function, however, manifested not only subjectively by vertigo but also objectively by a diminished or absent response to caloric stimulation, cannot be lightly regarded. It was almost constant in occurrence. It is certainly prolonged in its existence. It may be permanent. A certain degree of compensation occurred, but both the incidence and the degree of economic or social disability which it will entail must be determined by more prolonged observation of these patients. It was the judgment of the investigators that this phenomenon alone was sufficient to make inadvisable the use of streptomycin in minimal tuberculosis, or in any other tuberculous lesion which might be expected to respond to bed-rest alone or to other accepted forms of therapy. No progress was made by this investigation in localizing the pathological changes causing this unique and specific toxic effect. In its time of appearance, at least, it has proved to be a function of dosage (7) and, presumably therefore, of the plasma concentration of drug. It remains to be seen whether a shorter duration of treatment or a lower dosage regimen will diminish, or even obviate entirely, this phenomenon. These avenues are being explored by the Federal agencies which coöperated in the present investigation as they are by other investigators.

A second obstacle to successful therapy with streptomycin is the development of resistance to it by the tubercle bacilli. The precise time at which this resistance developed was not proved in the present study but it was present (to more than 10 mcg. per cc.) within sixty and ninety days in cultures from 65 per cent and at 120 days in cultures from 80 per cent of the patients from whom positive cultures could be obtained. Its extent is such as to make impossible any effective action upon the tubercle bacilli within the blood or tissues of these patients *if the bacilli in the body are as resistant to streptomycin as they are in vitro*. This conditional statement poses a prime problem in streptomycin therapy and one upon which the present study shed some light but, it must be admitted, scarcely illuminated. To determine the presence of resistance more rapidly and, once it is demonstrated, to continue or not to continue treatment, that is the question. It is temptingly rational to believe that *in vivo* and *in vitro* resistances parallel one another. Perhaps the strongest, though not a very precise, argument in its behalf is the fact that the most favorable progress in the pulmonary lesions occur in the first sixty to ninety days at a time when the organisms are susceptible *in vitro*, and the relapses and spreads occur after that time, when the organisms are often resistant *in vitro*. The Fitzsimons and Sunmount Units are of the opinion that their evidence favors the clinical significance of *in vitro* resistance, the Sampson Unit tends to be of the opposite opinion. It would require a long series of cases to determine the point; for resistant cases might well become worse, and sensitive cases become better, quite apart from whether they

receive streptomycin or not. There remains, also, the possibility that the organisms which, by growing, demonstrate their resistance are not typical of other organisms in the same specimen or elsewhere in the body, but are the few survivors of a larger number whose growth was, or would be, inhibited.

Accepting, for the purposes of this final paragraph, probability as fact—agreeing that the development of resistance *in vitro* indicates the futility of further treatment with streptomycin—it would be difficult to exaggerate its importance. There is no evidence as yet that organisms, once made resistant, can recover their susceptibility. As long as resistance persists, not only must the host be unsuitable for streptomycin therapy but anyone to whom he transmits his infection must be similarly unsuitable. This provides an additional argument for the investigators' present unwillingness to treat with streptomycin either minimal tuberculosis or any other lesion which may be expected to respond favorably to other forms of therapy. It was the province of the present study to confirm the existence and incidence of this resistance. No information was gained as to methods of avoiding it. If it be due to the multiplication of a few inherently resistant bacilli, no change in regimen could be useful and another drug must provide the answer. If, the alternative, it be an acquired resistance consequent upon exposure to streptomycin, a shorter course of treatment or even a lower dosage may offer a solution. These expedients are being studied by, amongst many others no doubt, the present investigators.

CONCLUSIONS

1. A total of 223 patients with moderately and far advanced pulmonary tuberculosis have been treated with streptomycin by a uniform regimen in seven Army, Navy and Veterans Administration hospitals. The results of this co-operative venture have been described in summary form, in this paper, under the several headings of roentgenographic, clinical, and laboratory observations. They are described, in proper detail, in the seven papers which follow it and to which it provides an introduction.

2. The roentgenographic changes, in more than half of the cases, were viewed by an impartial jury of plithisiologists, appointed for the purpose by the American Trudeau Society. It was the judgment of the jury that little or no change occurred in the productive or fibrocaseous lesions during the 120 days of treatment but that some degree of clearing occurred in 85 per cent of unstable, exudative lesions which had been unchanged or progressive in more than two-thirds of the cases for at least sixty days prior to streptomycin therapy. The judgment of the investigators, based on their consideration of the entire series, supported that of the jury. This quite uniform change in the trend of the disease is regarded as evidence that streptomycin can favorably affect pulmonary lesions of this character and that it is superior, in this respect, to the effects of bed-rest alone. It is not maintained that this roentgenographic clearing is often marked, or permanent. In point of fact, extension of lesions occurred in 8 per cent of cases towards the end of treatment in the present series and in 16 per cent during the first to fourth months following its completion. The incidence of sputum

conversion was of the order of 40 per cent. In the opinion of the investigators, the rôle of streptomycin in the treatment of pulmonary tuberculosis lies in the partial clearing of exudative lesions, either as an end in itself or as a preliminary to the collapse measures which it often makes possible.

3. The clinical changes during streptomycin therapy were as frequent in occurrence as the roentgenographic changes and more impressive in extent. Cough and the amount of sputum were almost constantly reduced; fever, when it was present, was similarly affected and more than 80 per cent of the patients gained an average in excess of 12 pounds in body weight.

4. The laboratory observations which accompanied this study established, or rather reaffirmed, two gross disadvantages of streptomycin therapy: the extraordinary and unique damage to the vestibular apparatus which it imposes and the development of a resistance by the tubercle bacilli which, in all probability, makes the long continuation of treatment unprofitable. The possibility of minimizing or avoiding these disadvantages by alterations of the regimen is being actively pursued.

CONCLUSIONES

Efecto de la Estreptomicina sobre la Tuberculosis Pulmonar: Informe Preliminar sobre 223 Enfermos

1. En 7 hospitales del Ejército, la Marina y la Administración de Veteranos han tratado con estreptomicina, usando un régimen uniforme, a 223 enfermos con tuberculosis pulmonar moderadamente o muy avanzada. En este trabajo describese, en forma sumariada, el resultado de esta empresa cooperativa, bajo los encabezados de observaciones radiográficas, clínicas y de laboratorio, reservándose los detalles para los siete trabajos siguientes, a los cuales sirve de introducción.

2. En más de la mitad de los casos, las alteraciones radiográficas fueron estudiadas por un jurado imparcial de tisiólogos, designado *ad hoc* por la Sociedad Americana de Trudeau, en cuya opinión hubo muy poca o ninguna modificación en las lesiones histógenas o fibrocásicas durante los 120 días de tratamiento, pero sí algún despejo en 90 por ciento de las lesiones exudativas, inestables, que no se habían modificado o se habían agravado en más de dos terceras partes de los casos por lo menos 60 días antes de la estreptomicinoterapia. El juicio de los investigadores, basado en el estudio de toda la serie, apoyó el del jurado. Esa alteración casi uniforme en la tendencia de la enfermedad se toma como prueba de que la estreptomicina puede afectar favorablemente las lesiones pulmonares del género mencionado, y que en ese sentido, supera los efectos del reposo en cama por sí solo. No se pretende que dicho despejo radiográfico sea a menudo pronunciado o permanente. En efecto, sobrevino difusión de las lesiones en 8 por ciento de los casos hacia el final del tratamiento en la serie actual y en 16 por ciento de uno a cuatro meses después de terminado. La frecuencia de la conversión del esputo llegó a 40 por ciento. A juicio de los investigadores, el papel de la estreptomicina en la tuberculosis pulmonar reside en el despejo parcial de

las lesiones exudativas, bien como meta definitiva o como paso preliminar para las medidas de colpaso que permite a menudo ejecutar.

3. Los concomitantes clínicos de la estreptomieinoterapia fueron tan frecuentes como las alteraciones radiográficas y más imponentes en su extensión. Disminuyeron casi constantemente la tos y la cantidad de esputo, la fiebre, cuando la había, se afectó en forma semejante, y más de 80 por ciento de los enfermos aumentaron, como promedio, más de 5.5 kg. en su peso.

4. Las observaciones de laboratorio que forman parte de este estudio establecieron, o más bien reafirmaron, la existencia de dos notables desventajas de la estreptomieinoterapia: el extraordinario y único daño que produce en el aparato vestibular y la formación de resistencia a la droga por el bacilo tuberculoso, lo que, con toda probabilidad, priva de provecho al tratamiento prolongado. Se investiga asiduamente la posibilidad de aminorar o evitar estas desventajas del régimen.

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ADDENDUM

As result of experience gained during the spring and summer of 1947, a daily dose of 1.0 gram of streptomycin, given in two intramuscular injections of 0.5 gram at twelve hour intervals, would appear to be quite as effective as the regimen described in this article, and certainly produces much less frequent damage to the eighth cranial nerve.

STREPTOMYCIN THERAPY IN PROGRESSIVE PULMONARY TUBERCULOSIS¹

Preliminary Report of Clinical Investigation in 37 Patients

R. O. CANADA²

In collaboration with

J. T. PITKIN,³ G. W. HEMSTEAD,⁴ G. JACOBSON⁵ AND WYLMA FUNK⁶

The Naval Hospital at Sampson, New York was chosen to represent the Navy in this coöperative study of pulmonary tuberculosis. Thirty-seven patients were selected with considerable care from approximately 1,500 tuberculosis patients, using the criteria which have been cited in the introductory paper of this series. This is a report of the immediate results of 120 days of streptomycin therapy in these 37 patients.

MATERIAL

All patients in this series were males between the ages of 18 and 41 years, with an average of 25.3 years. Thirty-one were white and 6 were Negro. Of the 31 white patients, 20 were in part or entirely of Irish antecedents. The patients had been on the sick list under observation and treatment for from three to twenty-three months. The average length of hospitalization before streptomycin treatment was 8.9 months. All except 2 patients presented roentgenographic evidence of recent progression in their pulmonary lesions. Of these 2, one had extensive exudative pulmonary involvement with increasing toxemia. The other had predominantly productive pulmonary disease with a complicating tuberculous enteritis. Both had shown previous progression of the pulmonary lesions. The disease was far advanced in 29 and moderately advanced in 8 in accordance with National Tuberculosis Association standards. No minimal disease was included. In each patient the sputum was positive for *Mycobacterium tuberculosis* on smear and culture within one month prior to instituting antibiotic therapy. Two patients presented an extensive hematogeneous distribution of pulmonary lesions without definite evidence of extrapulmonary tuberculosis. In addition to the exudative pulmonary disease, glandular and cutaneous tuberculosis was present in one, tuberculous empyema in 3 and tuberculous enteritis in 2. Six patients had a unilateral artificial pneumothorax which was being maintained at the time streptomycin therapy was instituted. In each of the latter, antibiotic therapy was directed toward disease in the contralateral lung. Two patients had had thoracoplasties and one a temporary phrenic interruption.

¹ From the U. S. Naval Hospital, Sampson, New York.

² Commander, M.C., U.S.N. Assistant Chief of Clinical Medicine.

³ Lieutenant Commander, M.C., U.S.N.

⁴ Lieutenant (jg), M.C., U.S.N.R. Department of Clinical Medicine.

⁵ Lieutenant Commander, M.C., U.S.N. Department of Radiology.

⁶ Lieutenant, W.R., U.S.N.R. Department of Clinical Pathology.

In only one instance had collapse therapy been instituted within less than three months prior to streptomycin therapy.

PROCEDURE

In addition to the laboratory procedures outlined in the protocol governing this study, the quantity of sputum was recorded daily. No new collapse therapy was deemed necessary during the course of treatment except in one instance (case VI), in which pneumothorax was instituted to control hemorrhage. The general hospital routine, including bed-rest, nursing care and diet, was maintained as closely as possible throughout the course of treatment.

Dosage: The daily dosage of streptomycin was the 1.8 g. prescribed in the protocol except that it was increased to 2.4 g. per day in 4 patients and to 3.0 g. per day in one who, during the course of treatment, showed evidence of increasing toxemia. The intramuscular administration was supplemented by a daily oral dose of one gram in the 2 patients with enteritis, by continuous local application in the one patient with cutaneous involvement and by streptomycin aerosol in 2 patients who presented evidence of endobronchial disease.

TOXEMIC REACTIONS

The toxemic reactions are summarized in table 1.

TABLE 1
Toxemic reactions

SEVERITY	VESTIBULAR DISTURBANCE	SKIN RASH	MOUTH LESIONS	FEBRILE REACTIONS	NAUSEA
Slight.....	24	2	0	14	7
Moderate.....	10	1	1	0	3
Severe.....	3	3	1	0	2
Total.....	37	6	2	14	12

Vestibular disturbance: Vestibular disturbance to some degree occurred in all 37 patients. In spite of the same dosage of streptomycin, this varied markedly in severity from slight dizziness to severe, almost constant vertigo with ataxia, nausea and vomiting. Vestibular disturbance was manifested most frequently by a dizzy or a light-headed sensation noted on sitting erect in bed, a feeling of falling to one side or the other, and an inability to focus the eyes after turning the head suddenly. Those patients who were permitted out of bed experienced difficulty in maintaining balance when walking. The onset of vestibular disturbance occurred earliest on the seventh day of treatment and latest on the seventy-fourth day, the average being thirty-one days. Dizziness continued with equal or increasing severity for an average of twenty-one days after which it gradually decreased. This symptom persisted at the completion of treatment in only 9 (24 per cent) of the 37 patients, whereas unbalance, as determined by inability to walk a straight line, persisted in 17 (60 per cent) of 28 patients tested. The

patients experienced no more difficulty maintaining balance while walking in darkness than in daylight. The Romberg test was positive in 2.

A modification of the Kobrak caloric test⁷ was used to determine vestibular function. Every patient had a normal response to caloric stimulation before antibiotic therapy. The response in each patient became abnormal with or shortly after the appearance of vertigo and remained abnormal at completion of treatment. The first abnormalities noted were delayed appearance time and decreased amplitude of nystagmus. Later nystagmus disappeared in all cases. Thirty-three patients have been observed for at least one month after completion of the course of antibiotic therapy and the response remains absent in all.

Auditory disturbance: Deafness did not occur in any patient. Two presented a transitory decrease of hearing in the high and 2 in the low tones as demonstrated by the audiometer. In none was this permanent or cause for decreasing the dosage. In fact, 2 patients showed an increase of hearing while under streptomycin therapy. Both had a chronic unilateral pyogenic otitis media. In neither could acid-fast organisms be demonstrated in the ear secretions. The hearing improved in the affected ear from a loss of 37 per cent to 19 per cent in one patient and from 78 per cent to 32 per cent in the other.

Skin rash: A generalized macular or maculo-papular skin rash occurred in 6 patients. The rash appeared on the sixth day of treatment in 2, the seventh day in 3 and the eighth day in one. In 3 the rash was severe and cause for interrupting treatment. In each of these 3, the rash faded promptly and, after small desensitizing doses, the former amount of streptomycin was resumed without recurrence of the rash. The less severe rash, noted in 3 cases, showed gradual clearing without decrease of streptomycin.

Two patients had a late toxemic manifestation. Both presented dry, chapped lips with fissuring, particularly in the corners of the mouth. One developed a swelling and redness of the tonsillar pillars, the other edema and redness of the pharynx and floor of the mouth. Both progressed to ulceration and membrane formation. These reactions appeared on the twenty-ninth and fifty-third days of treatment, respectively. Smears and cultures were negative for streptococci and Vincent's organisms. The white blood counts and differential smears were normal except that in each instance there was an increasing eosinophilia which preceded the appearance of the toxemic reaction. The lesions healed promptly when streptomycin was discontinued and reappeared in one case when the drug was resumed.

Febrile reactions: A mild febrile reaction occurred during the first nine days of

⁷ Procedure used in caloric test of vestibular function (modification of Kobrak test): Using a 20 cc. syringe with rubber nipple reaching almost to the ear drum and the patient in a sitting position with face straight forward, inject 15 cc. of ice water (from pan containing melting ice) over a period of thirty seconds. If the vestibular function is normal, nystagmus appears promptly toward the opposite side and is usually rotary. Turn head and face vertically and observe horizontal nystagmus to the opposite side. Nystagmus should be of one to two minutes duration. If the test is negative after the first injection, then inject 20 cc. of ice water over a period of thirty seconds and observe the patient in a similar manner.

treatment in 14 patients. This consisted of a rise in temperature of one to three degrees and lasted from two to five days. It was not regarded as cause for altering the treatment.

Nausea: Nausea and vomiting occurred in 12 patients and was thought due to the action of streptomycin either directly or indirectly. In 4 of these cases there was concomitant vertigo and it was difficult to determine the cause of nausea. The nausea continued for an average of three weeks.

Local reactions: All patients complained of moderately severe pain at the site of injection. Twenty-six patients, who had received penicillin injections previously, described the pain accompanying streptomycin injections as slightly more severe. Stiffness and soreness in the muscles at the site of injection occurred in every case and gradually subsided during the second and third weeks of treatment. No skin infections or subcutaneous abscesses developed.

One lot of streptomycin gave more severe local reactions, but otherwise there was no correlation between the toxemic reactions and lot of drug used.

TABLE 2
Changes in symptoms during treatment

CHANGES	ANOREXIA	COUGH	CHEST PAIN	WEAKNESS
Marked improvement.....	14	19	9	9
Moderate improvement	10	9	8	10
Slight improvement.....	9	4	3	3
No change.....	4	0	3	3
Worse.....	0	2	1	8
None in beginning.....	0	3	13	4
Total.....	37	37	37	37

RESULTS

Clinical observations: It is recognized that this new form of therapy produced a strong psychological effect in improving the morale and coöperation of the patient. However, symptomatic improvement was of such a degree that it seems unlikely this can be explained entirely on the basis of improved morale and better coöperation. As shown in table 2, all except 4 patients noted increased appetite. In 14 this was marked and the patients expressed a desire for abnormally large amounts of food, especially during the first month of treatment. Cough and expectoration decreased within the first two weeks in 32 patients. Weakness and fatigue decreased in the majority after the first month. Chest pain disappeared entirely in 9 patients in whom it had been a bothersome symptom. The patients all expressed a feeling of well-being.

The patients became more alert and showed a greater interest in their surroundings. This was particularly noticeable in those who had been the more toxemic. Weekly physical examinations of the chest revealed very little change in the findings, even in the instances where marked clearing in the roentgenograms was evident.

During the first month there was a consistent but gradual lowering of the temperature peaks by as much as 4.5°F. The average temperature of all cases was one degree lower than the pre-treatment level. The more toxemic patients showed the greater decrease in temperature. The temperature returned to normal and remained so in 17 cases, and to a stationary lower level in 15. In 5, after an initial drop, there was a slight increase later in the course of treatment. The average daily temperature peaks were 99°F. or higher in 34 of the 37 cases during the month prior to treatment as compared to 16 of the 37 cases during the last month of treatment. The pulse rate did not decrease in proportion to the temperature but remained at approximately the same level throughout the course of treatment.

There was a gain of weight in 33 of the 37 cases which ranged up to 45 pounds with an average gain of 14.2 pounds per patient. The maximum gain of weight occurred during the first month of treatment. All except 8 patients had had a progressive loss of weight in the three-month period prior to streptomycin therapy.

The average volume of sputum for all patients in the month prior to treatment was 75 cc. per twenty-four hours. During the first month of treatment this volume decreased to 45 cc. and, during the fourth and last month of treatment, it was 30 cc. per twenty-four hours. In general the sputum became less purulent and thinner. The frequency and severity of hemoptysis were unaltered during treatment, while in one patient it occurred for the first time.

Three patients were bronchoscoped prior to streptomycin therapy because of suspected endobronchial disease. In each instance, ulceration and acute inflammation were found in a major bronchus. One patient received streptomycin only intramuscularly and the other 2 received streptomycin aerosol in addition to intramuscular injections. Within a period of two months after treatment was started, bronchoscopic examination in all 3 cases demonstrated complete disappearance of the visible ulceration and inflammation.

Extensive glandular and cutaneous tuberculosis complicated by progressive pulmonary infiltrations was present in one patient (case III). Streptomycin was used intramuscularly and locally on the skin lesions with prompt symptomatic improvement. Rapid and complete healing of the extensive skin destruction and multiple draining sinuses occurred.

Two patients had tuberculosis of the terminal ileum, cecum and ascending colon. One patient (case IV) is presented below. Both had complete relief from severe intestinal symptoms after two weeks of oral and intramuscular streptomycin. One gained 24 pounds and the other 45 pounds during the four months of treatment.

Three patients had unilateral tuberculous empyema. In only one instance was there improvement thought due to streptomycin. This patient (case III) presented a draining empyema pocket which was irrigated with streptomycin solution. The sinus tract healed and the empyema pocket could not be seen on chest roentgenograms after three months of treatment. The 2 remaining patients received streptomycin only intramuscularly. Although there was no

further accumulation of fluid in the pleural space the fluid remained positive for *M. tuberculosis*.

Laboratory observations: The erythrocyte sedimentation rate (Cutler method) decreased more than 5 mm. per hour in 18 cases, remained approximately the same in 16 and increased one to 5 mm. in 3. The decrease of sedimentation rate appeared with other signs of improvement except in cases with extensive caseous involvement where the rate changed very little or increased slightly.

Complete blood counts were not remarkable except that all patients showed an eosinophil count in the differential smears of one to 5 per cent at some time during the course of therapy. This was considered within the normal range. However, in 17 cases (46 per cent) the count increased to between 5 and 29 per cent. Eosinophilia was of rather short duration in most cases. The 2 patients referred to under toxemic reactions, who presented mouth lesions, each had an increasing eosinophilia in the two-week period prior to the reaction. Otherwise, there was no correlation between the eosinophil count and the severity or onset of the other toxemic reactions.

The urine analyses were within normal limits except in several acutely ill patients each of whom had a transient albuminuria with cells and casts. There was no evidence of renal irritation which could be directly attributed to streptomycin. The urea clearance test used in this study was that of Moeller, McIntosh and Van Slyke. The results of this test, as obtained in this laboratory, were unreliable. Serial nonprotein nitrogen and blood urea determinations showed no nitrogen retention. There was no history to suggest prior renal damage in any of the patients treated.

The acid-fast bacterial count of sputum smears showed a continuous decrease in 17 of the 37 patients. Of these there were 8 who had negative smears and 3 who had negative smears and cultures of the sputum and gastric content at completion of treatment. In the remaining 20 patients there was no decrease of the bacterial count except that 4 had a transient decrease with subsequent rise.

The streptomycin blood levels were determined by the cup-plate method (1) using a sensitive strain of *Staphylococcus aureus* as the test organism. One or more blood level determinations were obtained on each patient during the course of treatment. Blood for the test was drawn one hour after a streptomycin injection. A total of 44 blood level determinations were made and the results are shown in table 3. The dosage of 1.8 g. per day produced an average blood concentration of 17.5 mcg. of streptomycin per cc. of serum at this time.

A detailed report of the sensitivity tests will be published at a later date. In order to better understand and interpret the results of the streptomycin sensitivity tests, a brief outline of the procedure (2) used in this laboratory is given. The test has two phases. The tubercle bacilli are first grown in broth containing various concentrations of streptomycin. After an interval of one to three weeks, the broth is examined for growth. The broth is then removed from the sediment, the latter washed twice with sterile saline, and poured on slants. The first phase shows the concentration of streptomycin which inhibits growth of the bacilli and

the second shows whether or not the bacilli are killed by this concentration. The broth^s used was one devised in this laboratory. An inoculum of 0.1 cc. of broth culture (reading between 35 and 40 on Klett-Summerson colorimeter) gives good growth in five to seven days. Petraghani's solid medium was used for the slants. Streptomycin sensitivity tests were performed in each case before therapy.

The bacilli from 26 patients were inhibited by 2 or less micrograms per cc. In 36 cases growth of the organism was inhibited by 20 or less micrograms of streptomycin per cc. of broth. This concentration of streptomycin approximated the average one-hour blood serum level of 17.5 mcg. per cc. In 13 cases the organisms, after being washed free of streptomycin, failed to grow when transferred to slants. In other words, when exposed in broth to streptomycin of the concentration obtained in the blood serum in this series, the organisms in all except one case were inhibited. However, when washed free of streptomycin and subcultured on solid media the bacilli from only 13 patients failed to grow. In 9 of the remaining 24 patients the bacilli were not killed by 200 mcg. per cc., which was the highest concentration used for sensitivity tests performed on bacilli

TABLE 3
Streptomycin blood serum level one hour after injection, in mcg. per cc.

TOTAL DAILY DOSE	NUMBER OF TESTS	HIGHEST	LOWEST	AVERAGE
grams				
0.9	1			
1.8	35	16.6		
2.4	6	26.2	—	—
3.0	2	24.2	9.0	17.5
		28.5	20.5	23.3
			25.0	26.8

obtained before treatment. This demonstrates the bacteriostatic and low bactericidal effect of streptomycin upon *M. tuberculosis*. There was no correlation between the clinical or radiological results and the sensitivity of these organisms. In 2 patients, multiple sensitivity tests were performed. The inhibition curve was of most value in estimating bacillary resistance. Resistance began in the second month of treatment. The increase was rapid and reached a peak during the third month when the number of acid-fast bacilli in the sputum smears was least.

^s Broth for culture of *Mycobacterium tuberculosis*:

Tryptose.....	20 g.
Sodium chloride.....	5 g.
Dextrose.....	5 g.
Asparagine.....	1 g.
Glycerine.....	50 cc.
Distilled water.....	1000 cc.

Heat the above named ingredients until the solids are dissolved. Dispense in 100 cc. amounts in 200 cc. flasks. Autoclave for twenty minutes at 15 pounds pressure. Before using, add 15 cc. of sterile serum which has been heated to 53° C. for thirty minutes to each 100 cc. broth. Dispense immediately in 5 cc. amounts into 16 by 150 mm. test tubes. Incubate for three days to test for sterility. Replace cotton plugs with corks.

The sensitivity of tubercle bacilli, isolated at completion of treatment, has been determined in only 13 cases. In 4, the bacilli were inhibited by concentrations of 50 to 1,000 mcg. per cc. and, in 9, the cultures grew in the presence of the highest concentration used which was 1,000 mcg. per cc. After exposure to 1,000 mcg. per cc. of streptomycin the bacilli grew on slants in all except one case.

At completion of treatment the bacilli were resistant to the action of streptomycin in all 13 patients. In only one of these were the bacilli killed by 1,000 mcg. per cc. Again, there was no correlation between clinical improvement and sensitivity of the organism. Streptomycin-fast bacilli were found in 4 patients, each of whom showed decrease of pulmonary infiltration during treatment but an increase of infiltration within the month following completion of treatment.

There was, however, a correlation between the rate of growth of the tubercle bacillus obtained during treatment and the clinical response of the patient. In general, good clinical results were seen in patients whose organisms grew slowly on artificial media. Poor clinical results occurred in patients whose organisms grew rapidly.

The tuberculin test was positive before treatment in all except 2 patients and in all patients at completion of treatment. Twenty showed a slightly stronger reaction and 2 a lesser reaction at completion of therapy. In the other cases, the reaction remained the same.

ROENTGENOGRAPHIC CHANGES

Serial roentgenograms were compared in each case. Evaluation of final results was based on those made before and after streptomycin therapy (table 4).

1. *New infiltrations:* New infiltrations were noted in only 2 cases.

The first (case VI) had a bronchogenic spread from the right apex to the right second anterior intercostal space; this occurred in a patient who developed continuously bloody sputum after one month of treatment. Pneumothorax, instituted at the end of the second month at which time the new infiltration was first seen, controlled both the spread and the hemoptysis but resulted in marked enlargement of the right apical cavities. Pronounced resolution of confluent infiltration in the left mid-lung field occurred during treatment.

The second new infiltration was observed in a patient (case V) who showed marked resolution of diffuse exudative infiltration in the right lower lobe with contraction and excavation in the right upper lobe. The roentgenogram made the day following the completion of therapy showed patchy infiltration in the left mid-lung field, the site of a previous contralateral spread. While this new lesion may have been a reactivation of the old, its appearance was more that of fresh contralateral spread following the excavation of the caseous right upper lobe.

2. *Exudative infiltrations:* Exudative infiltrations, a major criterion for selection, were observed in the chest roentgenograms of all patients. The immediate pre-streptomycin roentgenograms in 35 patients showed an increase in the

TABLE 4
Roentgenographic changes

	CHANGES DURING TREATMENT		PRESENT BEFORE TREATMENT		CHANGES DURING TREATMENT		PRESENT BEFORE TREATMENT
	degree	total			degree	total	
1. New Infiltrations.... (occurring during treatment)		2					
2. Exudative infiltrations.....			37	3. Proliferative infiltrations.....			33
A Disappeared.....		2		A Disappeared.....		0	
B Clearing.....		32		B Clearing.....		20	
Almost complete..	4			Almost complete..	1		
Marked.....	8			Marked.....	1		
Moderate.....	10			Moderate.....	7		
Slight.....	10			Slight.....	11		
C Unchanged.....		3		C More discrete....		6	
D Increased.....		0		D Unchanged.....		7	
				E Increased.....		0	
4. Consolidation			6	5. Atelectasis			10
Present before treatment.....				Present before treatment.....			
Developed during treatment.....		0		Developed during treatment.....		1	
A Resolution complete.....		0		A Increased.....	1	8	
B Resolution partial		6		Marked.....	4		
Marked.....	2			Moderate.....	3		
Moderate.....	1			Slight.....			
Slight.....	3			B Unchanged.....		2	
C Excavation.....		2		C Decreased.....		1	
6. Pleural fluid			6	7. Cavities			34
Present before treatment.....				Present before treatment.....			
A Decreased in amount.....		4		Developed during treatment.....		3	
Marked.....	2			A Closed.....		4	
Moderate.....	1			B Lost to view.....		3	
Slight.....	1			C Decreased in size.		17	
B Unchanged.....		2		Marked.....	3		
Developed during treatment.....		1		Moderate.....	7		
Slight.....	1			Slight.....	7		
				D Unchanged.....		5	
				E Larger.....		5	
				Marked.....	1		
				Moderate.....	2		
				Slight.....	2		

amount of exudative infiltration when compared to the roentgenograms taken within the preceding three months. After two weeks of treatment, the infiltration was considered to have decreased in 8 instances, to have increased in one

and to be unchanged in 28. Thereafter resolution was progressive, except in 3 patients whose infiltrations remained unchanged throughout the course of treatment.

Two patients showed dramatic and complete disappearance of the exudative component of their disease; one (case I) had extensive confluent disseminated pulmonary tuberculosis and the other (case III) had moderately advanced pulmonary tuberculosis without cavitation. Almost complete resolution was seen in 4 instances: one (case II) had a hematogenous involvement with contralateral spread; and one had moderately advanced exudative lesions. Eight were deemed to have marked resolution, 10 moderate and 10 slight resolution. Three remained unchanged. Except for the 2 patients whose roentgenograms showed new areas of infiltration, none showed an increase in size or density of existing exudative involvement.

3. *Productive infiltrations:* Productive infiltrations were frequently masked by exudative lesions to such an extent that no fair appraisal of the changes noted in the former could be made at the completion of treatment. In none was there complete disappearance of the productive element. In one (case III), there was almost complete clearing associated with complete disappearance of the exudative infiltration. There was marked clearing in one case, moderate clearing in 7, slight clearing in 11 and no change in 7. In 6 patients, the productive lesions were deemed to have become more discrete.

4. *Consolidations:* Lobar or segmental consolidation was present in 6 cases. In none did complete resolution occur. In 2 there was marked clearing, in one moderate clearing and in 3 slight clearing. Excavation occurred in 2 patients. One was accompanied by atelectasis of the involved lobe, and the other was followed by a contralateral spread.

5. *Atelectasis:* Atelectasis of some degree was present in 10 patients and developed during treatment in one. The degree of atelectasis of the involved area increased markedly and became complete in one, increased moderately in 4 and slightly in 3 cases; it was unchanged in 2 and decreased in one. The latter patient had endobronchial disease with air-trapping and partial atelectasis of the right upper lobe. Early in the course of treatment, the lobe became aerated although the enclosed cavities continued to vary in size. (Streptomycin aerosol was used in this case in addition to the intramuscular injections of streptomycin.)

6. *Pleural fluid:* Pleural fluid was present in 6 patients. At the completion of treatment the fluid was markedly decreased in 2 cases (one empyema, one serous effusion), moderately decreased in one with serous effusion and slightly decreased in one with empyema. In 2 cases it was unchanged (one empyema, one serous effusion). A small amount of serous fluid appeared in one patient.

7. *Cavities:* Cavities were present before treatment in 34 of the 37 patients. In 22 they were multiple. Cavity closure was noted in 4 patients. Two patients closed single cavities measuring 3.0 cm. and 1.5 cm., respectively. In the third, a cavity in the left mid-lung field closed, while there was contraction of the right upper lobe with a decrease in size of the enclosed cavities. In the fourth, multiple small cavities closed while the remainder were smaller.

A cavity was recorded as being lost to view when on serial roentgenograms it became progressively smaller and, while not clearly visible, it could not be stated with certainty that it was still present. There were 3 such cases. In these, the cavities were lost to view in atelectatic or partially atelectatic lobes.

The cavities were deemed to have decreased markedly in 3 patients, moderately in 7 and slightly in 7; they were unchanged in 5 patients. The cavities were slightly larger in 2 patients, moderately larger in 2 and markedly larger in one. In the last patient (case VI), there was air-trapping following an artificial pneumothorax. Decrease in the zone of reaction in the parenchyma surrounding cavities was a fairly consistent finding.

New cavities appeared in 3 patients who had cavitation before treatment. In all 3, the new cavities appeared in areas of confluent infiltration.

8. *Intestinal tuberculosis*: There were 2 patients in whom ileo-cecal tuberculosis was a severe complication. In each, barium studies of the gastro-intestinal tract showed extensive ulceration of the terminal ileum and cecum before the onset of streptomycin therapy. At the completion of treatment, one (case IV) had marked improvement with no roentgenological evidence of remaining active ulceration. The other developed a progressive fibrous contraction of the cecum, but had no evidence of active ulceration. While the mucosal pattern of the cecum and ileum showed less distortion and obliteration, in neither case did it return to normal.

AFTER-TREATMENT REACTIVATION

Six patients showed extensions of previous pulmonary infiltrations within one month after streptomycin therapy was discontinued. Reactivation occurred at the site of previous exudative infiltrations which had cleared markedly during therapy in 4 and had remained stable in 2. The underlying common factors which each case presented were:

- (a) Extensive exudative pulmonary infiltration.
- (b) Caseous tuberculosis of moderate or marked extent.
- (c) Total cavity diameter greater than 3 cm.
- (d) Sedimentation rate which decreased little or not at all during treatment.
- (e) A continuously high count of acid-fast bacilli as seen in the sputum smears.

Three of the 6 patients presented an increase of temperature and sputum volume during the third and fourth months of treatment. In all 6 cases, signs of increasing toxemia were present at the time reactivation was first evident in the roentgenograms.

A second course of streptomycin, consisting of 1.8 g. daily for from forty-five to ninety days, was given to 4 of these patients. Since the tubercle bacilli isolated from the sputa of each case were resistant to streptomycin at the time therapy was reinstituted, the results of this second course were observed with special interest. Data are available on 3 of the 4. In each instance there was definite symptomatic improvement during the first few weeks of the second course of treatment and in one, the others remaining unchanged, there was slight

but definite roentgenographic improvement. They have now been observed for from four to six months following completion of the second course of streptomycin and have been running a slowly but progressively downhill course.

CASE REPORTS

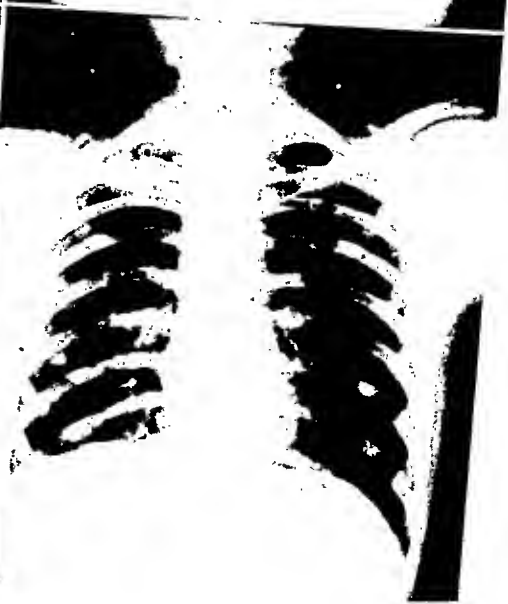
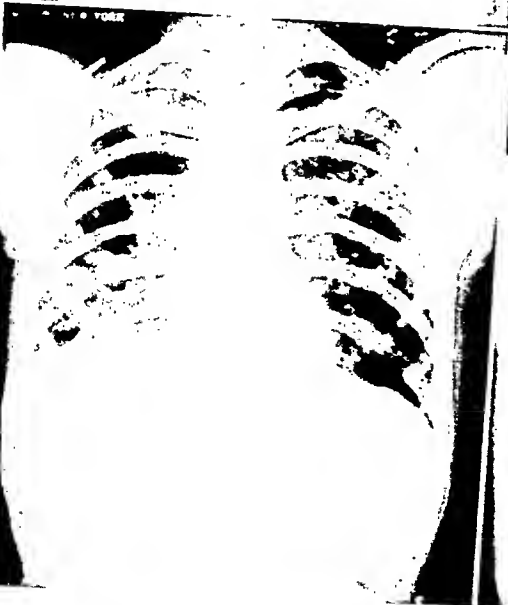
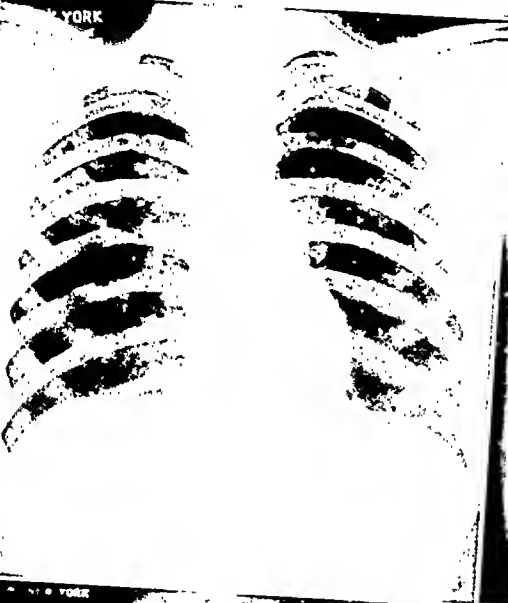
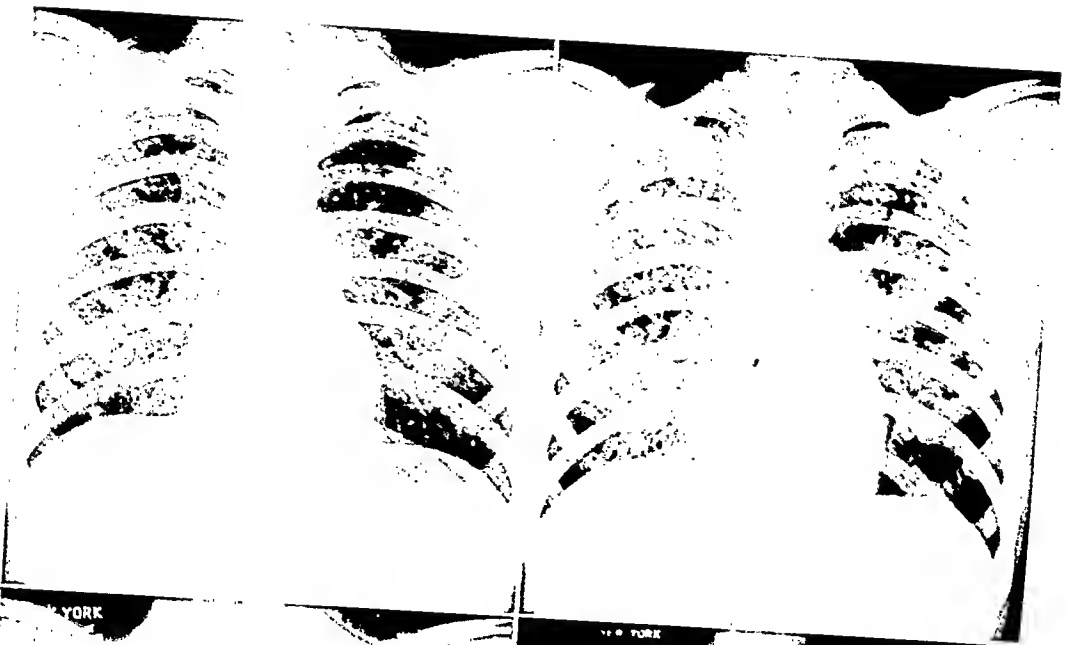
Case I: W. K., a 20-year-old white male, was admitted to a Naval hospital in March, 1946, following a brisk pulmonary hemorrhage. Direct smear and culture of his sputum were positive for *M. tuberculosis*. A chest roentgenogram taken 1 May 1946 showed extensive soft nodular infiltrations throughout both lung fields with multiple small cavities in the second anterior interspaces bilaterally (figure 1A). He was very toxemic with a daily temperature of 103°F. On 18 July 1946, he experienced a sudden onset of extreme toxemia characterized by temperature above 104°F., tachycardia, dyspnea, tachypnea, cyanosis and lethargy. A bed-side chest film, although not technically satisfactory, showed a marked extension of the diffuse infiltrative process in both lungs.

Treatment with streptomycin was begun on 25 July 1946 and continued for 124 days. A technically satisfactory chest roentgenogram was obtained on 18 August 1946, twenty-five days after treatment was started, (figure 1B) and showed acute dissemination of confluent nodular infiltrations involving the major portion of both lung fields. Symptomatic improvement was evident during the second week of treatment. Dyspnea, tachypnea and cyanosis disappeared and the temperature declined below 100°F. The patient became alert. During the third and fourth weeks, there was a gradual increase of temperature to 102°F. Dosage of streptomycin was increased after the fourth week from 1.8 to 2.4 g. per day. This was followed by a gradual decline of temperature to 99°F. where it remained for the duration of the treatment. The sputum decreased from 30 cc. per twenty-four hours to practically none by the seventh week. Although the patient had lost approximately 40 pounds in weight during the four months prior to treatment, he maintained a stable weight after treatment was begun.

A chest roentgenogram at completion of treatment (figure 1C) showed complete absorption of the diffuse nodular infiltrations in both lung fields. Small cavitation and surrounding infiltration, seen in figure 1A, remained in the second anterior interspaces bilaterally. The sputum continued positive. Tubercle bacilli isolated from the sputum at completion of treatment were resistant to streptomycin in concentrations of 1,000 mcg. per cc.

Case II: W. W. W., an 18-year-old white male, was admitted to a Naval hospital in May 1946 because of sudden onset of chills and fever. A chest roentgenogram showed a small area of exudative infiltration in the apex of the right lung and diffuse, fine, nodular infiltrations throughout both lungs, consistent with a hematogenous spread. By August 1946 (figure 2A), there had been an increase of the soft nodular infiltration with the appearance of fluid in the right minor interlobar fissure. There was also evidence of mediastinal lymphadenopathy. His clinical course was very toxemic with spiking temperatures of 102° to 104°F. daily. The patient lost 35 pounds between May and September 1946. He became quite lethargic. There were no neurological signs of meningeal irritation and spinal fluid examination was normal. The sputum, which had been minimal in amount, increased slightly and examination showed *M. tuberculosis* for the first time. A chest roentgenogram in September 1946, just prior to beginning treatment with streptomycin, (figure 2B) showed absorption of the interlobar fluid, but further extension of the soft nodular infiltrations throughout both lung fields.

Treatment with streptomycin was begun on 16 September 1946 and continued for eighty-seven days. Dosage was decreased from 1.8 to 0.9 g. per day between the fourth



and ninth weeks because of nausea and vomiting. During the remaining four weeks, 1.8 g. per day were administered. Treatment was discontinued during the twelfth week because of timitus and recurrence of nausea and vomiting. There was evidence of clinical improvement during the second week of treatment with decrease of cough and expectoration, decline of temperature peaks and disappearance of lethargy. The temperature returned to normal by the eighth week and remained so during the remainder of the treatment period. At completion of treatment, the sputum was negative by smear but positive by culture for *M. tuberculosis*. A chest roentgenogram (figure 2C) showed marked absorption of the nodular infiltrations and decrease in size of the mediastinal lymph nodes. The patient gained 8 pounds in weight during treatment.

Case III: J. B., a 22-year-old Negro male, was admitted to a Naval hospital in April 1945 because of cervical lymphadenopathy, which was later proved to be tuberculous by biopsy. A chest roentgenogram at that time showed no abnormality. Lymph nodes in the anterior and posterior cervical chains, submental, left preauricular, right epitrochlear and left femoral regions became enlarged, fluctuant and ruptured spontaneously. This resulted in local ulceration of the skin and draining sinuses. Extensive skin destruction occurred in the left cervical region. Exudate from the draining sinuses showed *M. tuberculosis*. A chest roentgenogram in October 1945 (figure 3A) showed an encapsulated empyema in the right upper thorax, but still no evidence of parenchymal infiltration. External drainage of the empyema pocket was accomplished and *M. tuberculosis* was isolated from the thick purulent contents. This was followed by an apparent rupture of the visceral pleura and infiltration of the adjacent lung parenchyma (figure 3B). The infiltration spread to involve the right hilum and both lower lobes by July 1946 (figure 3C). The sputum was positive by smear and culture. The clinical course became progressively more toxic between November 1945 and August 1946. The patient raised approximately 140 cc. of mucopurulent, odorless sputum daily. He had lost 45 pounds in weight and was extremely weak and unable to stand, even briefly. Treatment with streptomycin was begun on 1 August 1946, and continued for 120 days. Streptomycin was administered intramuscularly in dosage of 1.8 g. per day and applied

FIG. 1. Chest roentgenograms, in case I with advanced acute disseminated pulmonary tuberculosis.

A. (Upper left) May 1, 1946. Extensive nodular infiltrations throughout both lung fields with multiple small cavities in the second anterior interspaces bilaterally.

B. (Upper right) August 19, 1946. At beginning of treatment with streptomycin. Acute dissemination characterized by soft, confluent, nodular infiltrations.

C. (Centre left) November 26, 1946. At completion of treatment with streptomycin. Complete absorption of diffuse, soft, nodular infiltrates. Cavitation and surrounding infiltration remain in the second anterior interspaces bilaterally.

FIG. 2. Chest roentgenograms, case II with lymphohematogenous pulmonary tuberculosis.

A. (Centre right) August 5, 1946. Extensive soft nodular infiltrations throughout both lungs. Confluent exudative infiltration at the right apex. Fluid in right minor interlobar fissure. Mediastinal lymphadenopathy.

B. (Lower left) September 12, 1946. At beginning of treatment with streptomycin. Further extension of soft nodular infiltrations in both lungs. Absorption of interlobar fluid on the right.

C. (Lower right) December 23, 1946. At completion of treatment with streptomycin. Pronounced absorption of diffuse nodular infiltrates. Moderate resolution of confluent exudative lesion at right apex. Decrease in mediastinal lymphadenopathy.

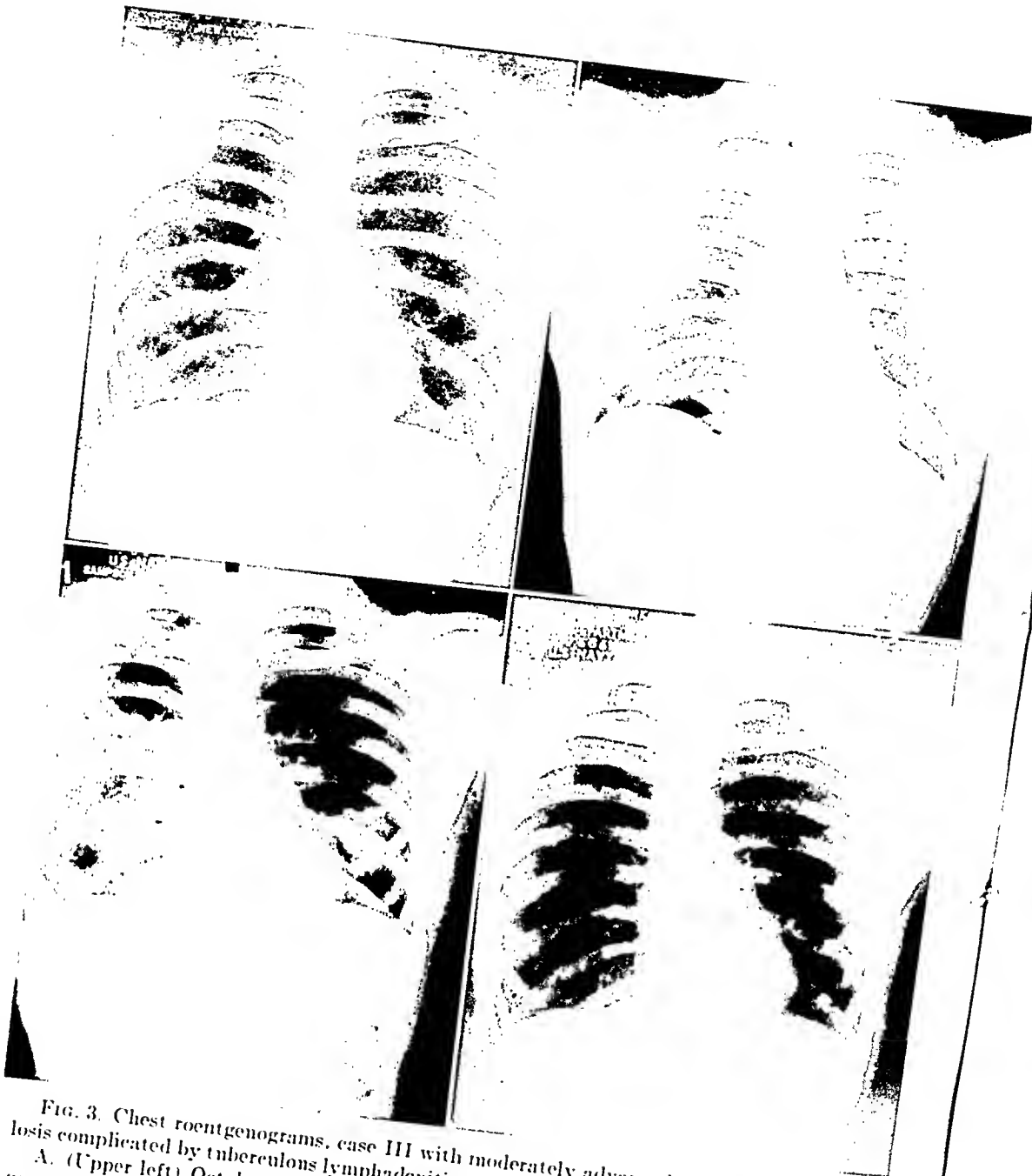


FIG. 3. Chest roentgenograms, case III with moderately advanced pulmonary tuberculosis complicated by tuberculous lymphadenitis and empyema.

A. (Upper left) October 16, 1945. Encapsulated empyema in right upper thorax. No parenchymal infiltration is evident.

B. (Upper right) November 1, 1945. Open drainage of empyema pocket was followed by infiltration in subjacent lung parenchyma. Thick empyema fluid positive for *M. tuberculosis*.

C. (Lower left) July 23, 1946. At beginning of treatment with streptomycin. Spread of infiltrations to right hilum and both lower lung fields. Sputum positive for *M. tuberculosis*.

D. (Lower right) December 13, 1946. At completion of treatment with streptomycin. Complete resolution of parenchymal infiltrations except for a minimal amount of productive disease in the left lower lung field. Thickening of the right lateral pleura remains.

locally to the skin lesions in 1:1000 solution as continuous wet dressings. The empyema pocket was irrigated once daily with the 1:1000 solution of streptomycin. Marked symptomatic improvement occurred during the first month of treatment. Appetite improved and the patient gained 9 pounds in weight. Cough and expectoration decreased with sputum volume falling to less than 30 cc. per day. The temperature returned to normal. Grossly, there was complete healing of the multiple draining sinuses after thirty days' treatment, except for the large area of skin destruction in the left cervical region where clean granulation tissue and rapid marginal epithelization was apparent. By the end of the four-month period of treatment, this area was completely covered with epithelium and firm underlying scar. A chest roentgenogram taken after completion of treatment (figure 3D) showed complete resolution of the parenchymal infiltration, except for a minimal amount of productive involvement in the lower lobe of the left lung. Thickening of the right lateral pleura remained. The sputum and gastric contents were negative by smear and culture. The patient gained 32 pounds in weight during treatment.

Case IV: T. A. B., a 25-year-old white male, was admitted to a Naval hospital in December 1944 and found to have moderately advanced, active, pulmonary tuberculosis. Because of cavitation in the upper lobe of the left lung and unsuccessful attempts to establish pneumothorax, a left thoracoplasty was performed in August 1945. Two months later, in October 1945, the patient developed severe abdominal cramping and diarrhea with passage of eight to fourteen watery stools per day. These symptoms persisted and the patient lost approximately 40 pounds in weight during the next nine months. In July 1946 he was quite weak, cachectic and weighed 99.5 pounds (figure 4A). The sputum and stools contained *M. tuberculosis*. Contrast studies of the intestinal tract in May 1946 (figure 5A) showed extensive ulceration of the terminal ileum, cecum and ascending colon, with marked local tenderness and irritability. A chest roentgenogram in May 1946 showed left thoracoplasty and exudative infiltration in the apex of the right lung enclosing a cavity measuring 1.5 cm. in diameter. By July 1946, just prior to starting treatment with streptomycin, there had been a slight increase of the infiltration in the right first and second anterior interspaces.

Treatment with streptomycin was begun on 1 August 1946 in dosage of 1.8 g. per day intramuscularly, and 1.0 g. per day by mouth. This treatment was continued for the next 120 days. Within the first two weeks of treatment, there was marked symptomatic improvement with cessation of abdominal cramps and diarrhea. For the first time in nine months, the patient had only one or two semi-solid bowel movements per day. He developed a ravenous appetite and promptly began to gain weight, at the rate of 4 or 5 pounds per week. The total gain during the 120 days of treatment was 45.5 pounds. The temperature peaks had declined from 100.6° to 99.0°F. by the fourth week and became normal after the fourteenth week. Contrast studies of the intestinal tract at completion of treatment (figure 5B) showed the mucosal pattern of the cecal area to be distorted and partially obliterated, but the bowel was no longer irritable and there was no evidence of active ulceration. A chest roentgenogram showed slight absorption of the infiltration in the upper lobe of the right lung and decrease in size of the cavity within the circle of right first rib. *M. tuberculosis* could not be identified in smears, but grew from cultures of the sputum.

Case V: A. S., a 21-year-old Negro male, was admitted to a Naval hospital in March 1946, complaining of sudden onset of cough, chest pain, chills and fever. Direct smears of his sputum were positive for *M. tuberculosis*. A chest roentgenogram, on admission, showed

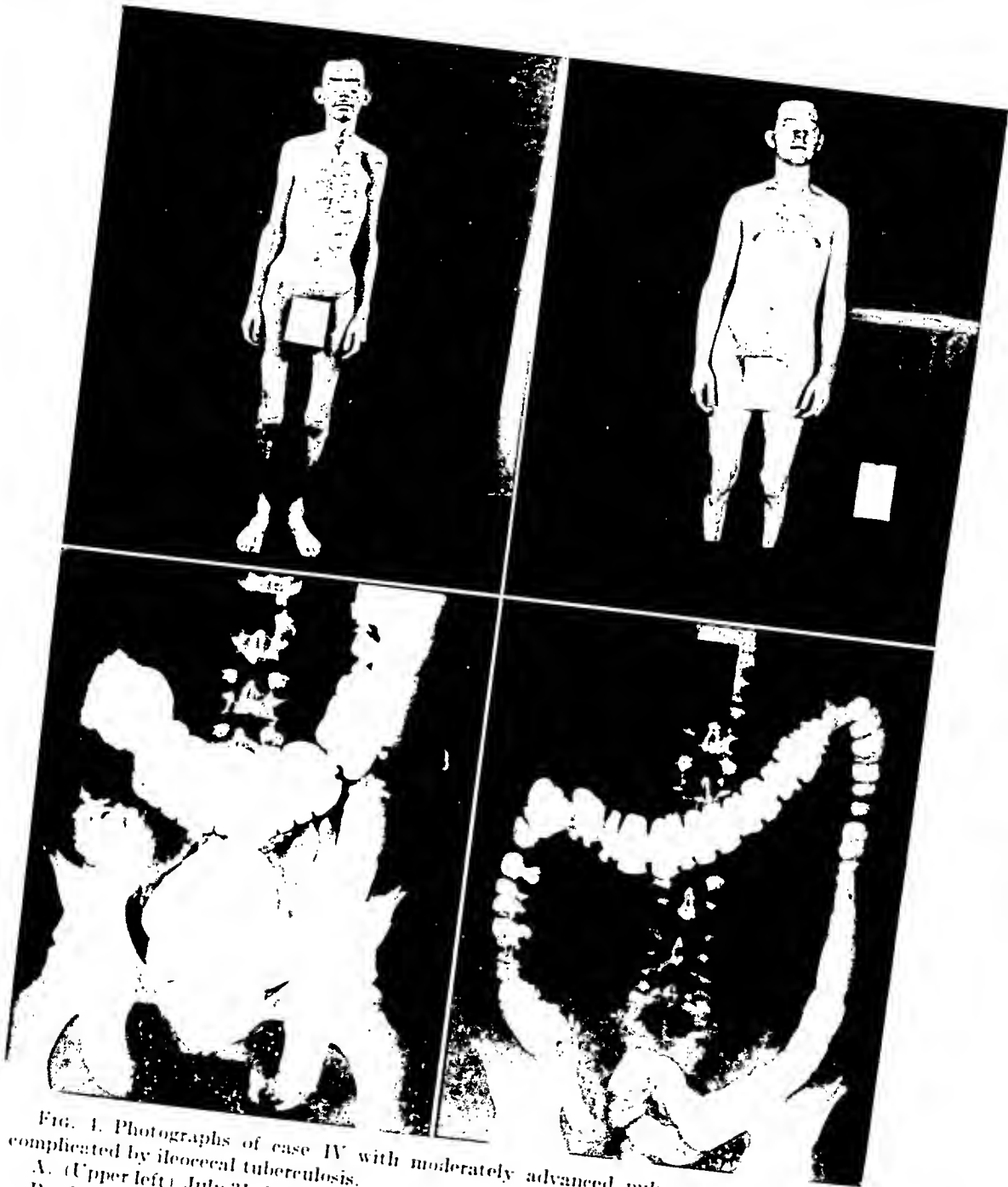


FIG. 4. Photographs of case IV with moderately advanced pulmonary tuberculosis complicated by ileocecal tuberculosis.
 A. (Upper left) July 31, 1946. At beginning of treatment with streptomycin.
 B. (Upper right) January 23, 1947. At completion of treatment with streptomycin.

FIG. 5. Contrast studies of intestinal tract of case IV.
 A. (Lower left) May 22, 1946. Before treatment with streptomycin. Extensive ulceration of the terminal ileum, cecum and ascending colon. Irritability of bowel and marked tenderness to palpation in this region.
 B. (Lower right) December 17, 1946. At completion of treatment with streptomycin. The mucosal pattern remains distorted and partially obliterated; however, the bowel is no longer irritable or tender to palpation, and there is no evidence of active ulceration.

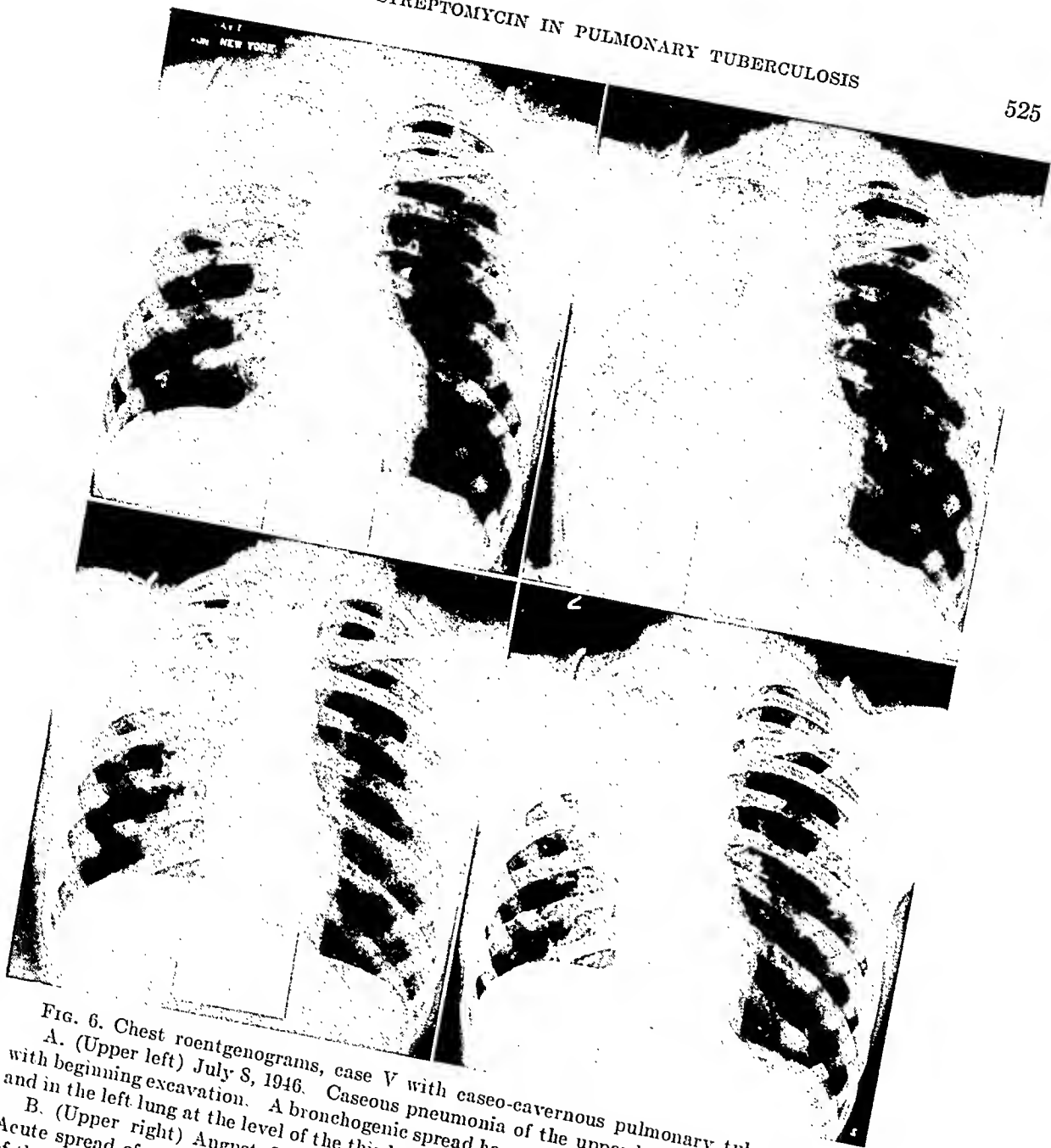
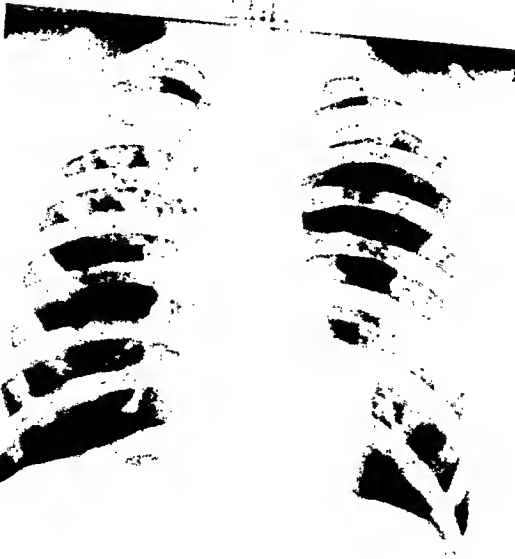
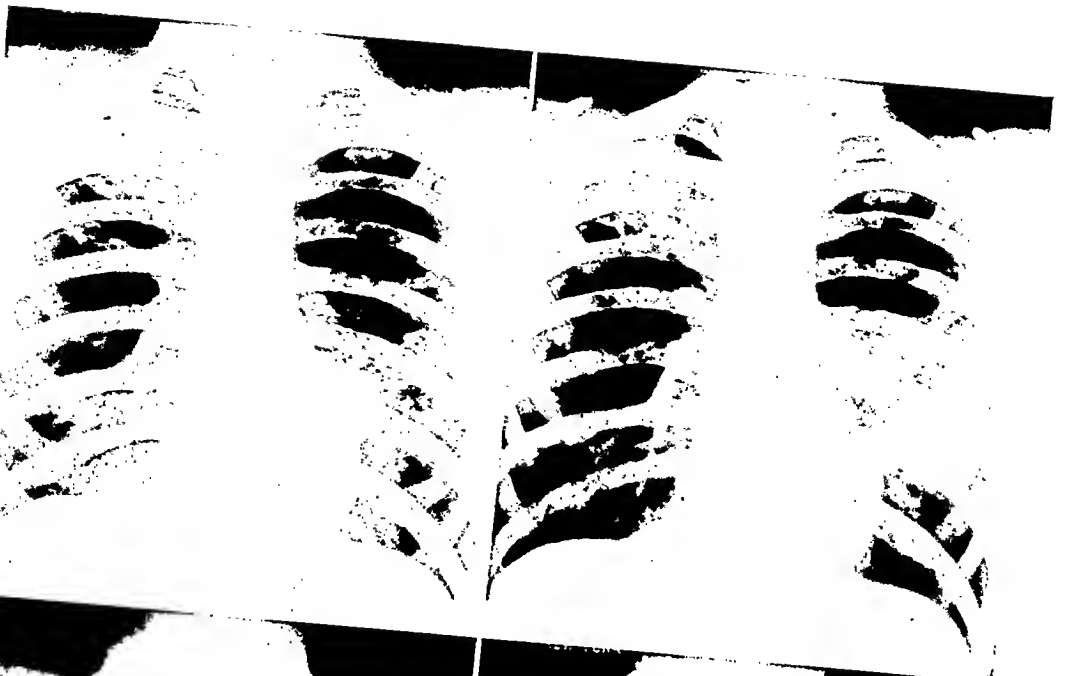


FIG. 6. Chest roentgenograms, case V with caseo-cavernous pulmonary tuberculosis.

- A. (Upper left) July 8, 1946. Caseous pneumonia of the upper lobe of the right lung with beginning excavation. A bronchogenic spread has occurred at the right base medially and in the left lung at the level of the third anterior intercostal space.
- B. (Upper right) August 22, 1946. At beginning of treatment with streptomycin. Acute spread of soft nodular infiltrations to entire right lower lung field with thickening of the overlying pleura.
- C. (Lower left) December 18, 1946. One week before completion of treatment with streptomycin. Marked resolution of nodular infiltration in the right upper lobe has occurred and small radiotranslucent areas have appeared below the right minor interlobar fissure.
- D. (Lower right) December 27, 1946. At completion of treatment with streptomycin. Additional spread to the left mid-lung field has appeared.



extensive soft exudative infiltration confined to the upper lobe of the right lung. The infiltration became confluent and by July 1946 (figure 6A) there was partial consolidation of the right upper lobe with caseation and excavation. A bronchogenic spread had occurred in the right base medially and in the left mid-lung field. His clinical course was very toxic with temperature spiking to between 102° and 104°F. daily. Between June and August 1946 the patient lost 27 pounds in weight. A chest roentgenogram taken in August 1946 (figure 6B), just prior to starting treatment with streptomycin, showed an acute spread of soft nodular infiltrations to the entire right lower lung field and thickening of the overlying pleura.

Treatment with streptomycin was begun on 28 August 1946 and continued for a period of 120 days. During the first two weeks of treatment there was a gradual decline of the temperature peaks from 102.6° to 99.6°F. and symptomatic improvement. This continued until after the eighth week of treatment when the temperature began to rise slowly and attained peaks of 101° to 102.8°F. by completion of treatment. The weight, which had been declining rapidly prior to treatment, remained stationary for three months and then, during the last month of treatment, he lost 8 pounds. A chest roentgenogram taken eight days before discontinuing treatment with streptomycin (figure 6C) showed marked resolution of the nodular infiltrations in the right lower lung field. Further excavation of the right upper lobe had occurred and small areas of radiotranslucency had appeared below the minor interlobar fissure. Nine days later (figure 6D), further contralateral spread to the left mid-lung had occurred. The sputum remained positive.

Case VI: J. M. K., a 23-year-old white male, was admitted to a Naval hospital in May 1946, complaining of fever, cough, expectoration and weakness. Direct smears and cultures of his sputum were positive for *M. tuberculosis*. A chest roentgenogram in July 1946 (figure 7A) showed exudative and productive infiltrations in the upper lobe of the right lung, enclosing several cavities and a patchy, exudative bronchogenic spread in the left mid-lung field. The clinical course was very toxic with daily temperature peaks of 101°F. The patient lost 38 pounds in weight between December 1945 and August 1946. A chest roentgenogram in August 1946 (figure 7B) showed enlargement of the cavities in the upper lobe of the right lung, and confluence of the infiltrates in the mid-portion of the left lung.

Fig. 7. Chest roentgenograms, case VI with moderately advanced pulmonary tuberculo-
sis.

- A. (Upper left) July 9, 1946. Exudative and productive infiltrations in the upper lobe of the right lung, enclosing multiple cavities. A soft patchy bronchogenic spread is present in the left mid-lung field.
- B. (Upper right) August 8, 1946. At beginning of treatment with streptomycin. Confluence of exudative infiltrates in the left mid-lung has occurred.
- C. (Centre left) November 5, 1946. During the eleventh week of treatment with streptomycin. Pronounced resolution of the disease in the right second anterior intercostal space. New areas of infiltration have appeared in the right upper lobe cavities. Further clearing of infiltrates on the left.
- D. (Centre right) December 16, 1946. During the seventeenth week of treatment. Right artificial pneumothorax has been instituted which controlled pulmonary bleeding, but resulted in air trapping and enlargement of the right upper lobe cavities. Further clearing of infiltrates on the left.
- E. (Bottom) January 13, 1947. One week after discontinuing treatment with streptomycin. Pneumothorax has been discontinued, but cavities in the right upper lobe remain large. Infiltrates in the middle of the left lung have increased.

Treatment with streptomycin was begun on 14 August 1946, and continued for 145 days. There was a decline of temperature and weight gain through the ninth week of treatment. His sputum was bloody almost continuously between the eighth and thirteenth weeks. A chest roentgenogram during the eleventh week (figure 7C) showed new infiltrates in the right lung at the level of the second anterior interspace, while those in the left lung had cleared considerably. Right artificial pneumothorax was induced during the twelfth week in an effort to control the hemorrhage, which was thought to have its origin in the cavities contained in the upper lobe. Bleeding stopped promptly; however the cavities in the upper lobe were seen to enlarge, probably due to air trapping (figure 7D). Because of this, pneumothorax was discontinued during the eighteenth week. Treatment with streptomycin was discontinued after twenty-one weeks. A chest roentgenogram one week later (figure 7E) showed increased infiltration in the left mid-lung. The sputum remained positive. Tubercle bacilli isolated from the sputum were sensitive to 2 meg. of streptomycin per cc. before treatment was begun. At the end of the fourth week, the bacilli from the sputum were inhibited by a minimum of 50 meg. per cc. and at completion of 145 days of treatment with streptomycin, the bacilli were resistant to 1,000 meg. per cc., the maximum concentration used in the test.

DISCUSSION

All 37 patients selected for streptomycin therapy had exudative pulmonary tuberculosis, either alone or in combination with other forms of the disease. Thirty-five of these had shown progression of the pulmonary infiltration within the three-month period preceding the beginning of streptomycin therapy. The remaining 2 had relatively stable pulmonary disease but had other signs of progressive tuberculosis. *It should be emphasized that all patients in this series had pulmonary tuberculosis which, prior to streptomycin therapy, had not responded to bed-rest or other accepted forms of treatment.*

In 31 (84 per cent) of the cases there was symptomatic improvement, with increase in weight, decrease in temperature and decrease in sputum volume within the first month of treatment. These changes were marked in 13 (35 per cent). After the first month, improvement was more gradual. Six patients (16 per cent) showed little or no clinical change throughout the course of treatment. Four additional patients had clinical improvement in the first and second months of treatment. Increase of streptomycin dosage in these patients produced only temporary improvement. However, 27 patients (73 per cent) showed continued clinical improvement. It is well known that symptomatic improvement in tuberculosis frequently attends any new form of therapy. However, we believe the improvement noted cannot be explained entirely on this basis.

The most marked resolution noted in the chest roentgenograms occurred in the soft nodular and exudative types of infiltrations and was seen in 34 of the 37 patients. In 8 patients, beginning resolution was evident by the end of the second week. Consolidations and confluent infiltrations of fairly recent occurrence showed moderately good response to therapy, whereas similar lesions of long standing showed very little response. In the latter type of disease one might expect to find caseation and tissue destruction well established. Where

there was evidence of caseation, new excavation occurred in 3 cases and old excavation increased in 4. The zone of acute reaction about cavitation frequently showed clearing and was followed by decrease of the diameter of the cavity. Cavities became smaller in 17 and were closed or lost to view in 7 patients.

All of these changes might be expected in the normal process of healing in tuberculosis, that is, the acute exudative disease heals rapidly whereas the older disease processes, with destruction of tissue and fibrosis, heal more slowly. However, in the acute disease areas, not only was progression of the disease halted but resolution of some degree occurred in 34 of the 37 cases.

In caseous tuberculosis there is tissue destruction and frequently a surrounding fibrous capsule (3) which interferes with good blood supply to the involved area. Also there is interference with the presence of fibrosis. These factors tend to decrease the concentration of streptomycin reaching the diseased areas. In acute exudative infiltrations there is little tissue destruction and little interference with the blood supply. This may explain, at least in part, the better results obtained in the latter type of disease.

In 2 patients, new areas of infiltrations appeared during treatment, one following a prolonged pulmonary hemorrhage and the other following massive excavation of a caseous lobe. In each instance there probably was a massive bronchogenic implant of bacilli which resulted in the new lesions.

It has been shown (4, 5, 6) that streptomycin exerts a suppressive action on *M. tuberculosis in vitro* and *in vivo*. That this action is bacteriostatic and not bactericidal in the concentrations of streptomycin obtained in the blood-stream, is supported by the fact that the disease process was apparently inhibited in 6 cases during treatment only to progress when the drug was discontinued.

Streptomycin in dosage of 0.3 g. every four hours produced a blood serum concentration in the first hour after injection (average 17.5 mcg. per cc.) which is almost nine times the concentration required to inhibit the growth *in vitro* of the strains of *M. tuberculosis* isolated from the majority of these patients. Resistance to the action of streptomycin developed rapidly in 2 cases tested, and the tubercle bacilli were found resistant after thirty days of treatment. Resistant action of streptomycin in concentrations of 30 mcg. per cc., a figure almost twice the average blood serum concentration. It was noted that clinical improvement was not so marked or rapid after the first thirty days of treatment. This may represent the point at which the bacterial resistance rises above the effective blood level of streptomycin. However, in the majority of cases, clinical and roentgenographic improvement continued beyond thirty days. It is quite possible that this short period of inhibition is sufficient to allow the patient's resistance to increase and continue the healing processes. Even though the *in vitro* tests indicate resistant bacilli, it would seem that streptomycin serves to prevent further spread of the disease in the majority of cases. It has been stated by Hinshaw *et al.* (7) that tuberculous meningitis frequently responds to a second course of streptomycin. Our experience with a second course of treatment of

exudative pulmonary tuberculosis in 3 patients with resistant organisms has, however, been disappointing.

It is quite possible that the dosage of streptomycin may have been greater than necessary to produce good clinical results. It is also possible that, in less extensive disease, 120 days of treatment may have been longer than necessary. In other instances the converse may have been true. Certainly, in 6 cases there was reactivation of the disease after 120 days of treatment. Additional study using varied dosage, in different types of tuberculosis, and over varying periods of time, is necessary to answer this question.

It was judged, before treatment, that 24 of the 37 patients would require thoracoplasty if their acute disease process could be controlled and their general condition improved. At the completion of treatment 7 patients were considered ready for surgery, 3 were almost ready and 6 had improved to such an extent that no collapse measures were deemed necessary. In these cases, streptomycin was a valuable method of treatment. Further study is indicated to determine the value of streptomycin, as an adjunct to bed-rest, in shortening the time interval these patients must wait before collapse measures can be instituted.

Toxic reactions to streptomycin were not serious and in only 2 cases were they cause for discontinuing treatment in less than 120 days. One case had an ulcerating lesion in the mouth and the other had severe nausea, vomiting and tinnitus. These reactions are potentially serious and require careful observation of the patient. Vestibular disturbance occurred in all patients. Subjective and objective vertigo appeared about the end of the first month and continued for an average of three weeks, after which there was improvement. Response to the caloric test of vestibular function became abnormal during the second month and subsequently disappeared. This response remained absent in all patients observed, for at least one month after completion of therapy. With one exception, those patients whose physical condition permitted them to be ambulatory at completion of treatment experienced little or no difficulty in walking either in daylight or darkness. However, as reported by Brown and Hinshaw (8), there appears to be damage to the vestibular apparatus which remains after prolonged streptomycin therapy has been discontinued.

SUMMARY

1. Thirty-seven patients with exudative pulmonary tuberculosis, either alone or in combination with other forms of the disease, were treated with streptomycin in dosage of 1.8 g. per day for a period of 120 days. There were minor variations in dosage and length of treatment.
2. Symptomatic improvement and decrease of toxemia, as evidenced by less cough and expectoration, decline of temperature, improvement of appetite and gain in weight, occurred during the first month of treatment in 31 (84 per cent) of the patients. Thereafter, improvement was more gradual but continuous in all except 4 patients who became more toxemic during the third and fourth months of treatment. The remaining 6 patients (16 per cent) showed little or no clinical improvement throughout the course of streptomycin therapy.

3. The number of tubercle bacilli in the sputum decreased in approximately 50 per cent of the patients treated, as judged by absent or fewer bacilli in serial smears of the sputum. In only 3 patients was there failure to identify *M. tuberculosis* by culture of sputum and gastric contents at completion of treatment with streptomycin.

4. The concentration of streptomycin equivalent to the average one-hour blood serum level (17.5 mcg. per cc.) was bacteriostatic but, as a rule, not bactericidal for the tubercle bacilli isolated from the patients before treatment. Tubercle bacilli, isolated from 13 patients at completion of treatment, were examined and found to be approximately 500 times more resistant to the inhibiting action of streptomycin. This, however, was not incompatible with a good clinical and roentgenographic response to treatment in several of these cases.

5. Although 35 patients had roentgenographic evidence of progressive pulmonary infiltration during the three-month observation prior to streptomycin therapy, there was no further extension of preëxisting infiltration during treatment. Small areas of infiltration, appearing to be bronchogenic spreads, occurred in 2 instances. There was extension of infiltration in 6 patients within one month after treatment with streptomycin was discontinued.

6. Resolution was more pronounced in the exudative and soft nodular types of pulmonary infiltration. Absorption of the productive type of infiltration was observed, but was less marked. Fibro-caseous disease showed very little change.

7. Pulmonary cavities decreased in size or closed in 70 per cent of the patients treated. From 24 patients having large cavities at beginning of treatment, it was considered that thoracoplasty probably had been averted in 6, and 7 others were improved to such an extent that surgery could be performed.

8. The toxemic reactions to streptomycin were not alarming. Skin rash, mucous membrane ulceration or nausea and vomiting were cause for interrupting treatment temporarily in 3 patients and for discontinuing treatment in 2 others. Disturbance of equilibrium occurred in every patient. Dysfunction of the vestibular apparatus, as determined by the caloric test, developed insidiously and remained for at least one month after completion of treatment.

SUMARIO

La Estreptomicinoterapia en la Tuberculosis Pulmonar Evolutiva: Investigación Clínica

1. Treinta y siete enfermos con tuberculosis pulmonar exudativa, ya sola o combinada con otras formas de la dolencia, fueron tratados con estreptomicina a dosis de 1.8 gm. diarios durante un período de 120 días, aunque hubo pequeñas variaciones en la posología y la duración del tratamiento.

2. Durante el primer mes del tratamiento hubo en 31 enfermos (84 por ciento) mejoría sintomática y disminución de la toxemia, expresadas en forma de menos tos y expectoración, baja de la temperatura, mejor apetito y aumento de peso. A partir de entonces, la mejoría fué más paulatina pero continuó en todos los pacientes, menos 4, que se volvieron más toxémicos durante el tercer y el cuarto

meses de tratamiento. Los otros 6 enfermos (16 por ciento) revelaron muy poca o ninguna mejoría clínica durante toda la serie de estreptomycinoterapia.

3. El número de bacilos tuberculosos en el esputo disminuyó aproximadamente en 50 por ciento de los enfermos tratados, a juzgar por la falta o descenso de los gérmenes en frotis seriados del esputo. Sólo en 3 enfermos no se pudo identificar el *M. tuberculosis* mediante el cultivo del esputo y el contenido gástrico al terminar el tratamiento con estreptomicina.

4. Una concentración de estreptomicina equivalente al nivel hemosérico medio en una hora (17.5 megm. por cc.) resultó bacteriostático, pero por regla general no bactericida para los bacilos tuberculosos aislados de los enfermos antes del tratamiento. Los bacilos aislados de 13 enfermos al terminar el tratamiento fueron estudiados, mostrándose unas 500 veces más resistentes a la acción inhibidora de la droga, pero esto no resultó incompatible con una buena respuesta clínica y radiográfica al tratamiento en varios de esos casos.

5. Aunque 35 enfermos tenían signos radiográficos de infiltración pulmonar evolutiva durante los tres meses de observación anteriores a la estreptomycinoterapia, no hubo más difusión de la infiltración preexistente durante el tratamiento. En 2 casos sobrevinieron pequeñas zonas de infiltración, aparentemente de propagación broncógena. En 6 enfermos había extensión de la infiltración en término de un mes después de suspenderse la estreptomycinoterapia.

6. La resolución fué más pronunciada en las formas exudativa y nodular blanda de la infiltración pulmonar. También se observó, pero en menor grado, absorción de la infiltración de tipo exudativo. La forma fibrocásica mostró muy poca modificación.

7. En 70 por ciento de los enfermos tratados las cavernas pulmonares disminuyeron de tamaño o se cerraron. A juzgar por 24 enfermos que tenían cavernas grandes al principio del tratamiento, se evitó probablemente la toracoplastia en 6 y otros 7 mejoraron a tal punto que pudieron ser operados.

8. Las reacciones tóxicas a la estreptomicina no fueron alarmantes. La aparición de eritema, ulceración de las mucosas o náuseas y vómitos hicieron suspender el tratamiento temporalmente en 3 enfermos y abandonarlo en otros 2. En todos los enfermos hubo trastornos del equilibrio. La disfunción vestibular, según se determinó con la prueba del calor, apareció insidiosamente y continuó por lo menos un mes después de terminar el tratamiento.

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STREPTOMYCIN AND BED-REST IN THE TREATMENT OF PULMONARY TUBERCULOSIS^{1,2}

MYRON W. FISHER,³ GEORGE W. FISHBURN⁴ AND JOHN B. WALLACE⁵

Since June 1946, some 250 patients with various types of tuberculosis have been treated with streptomycin at Fitzsimons General Hospital. The present report deals only with the 79 patients with pulmonary tuberculosis who have been treated under the terms of the protocol designed by the coöperating Federal agencies, namely by streptomycin and bed-rest alone without ancillary collapse procedures.

CLINICAL MATERIAL

Of the 79 patients in this group, 44 were white, 33 Negroes and 2 Orientals. There were 76 males and 3 females. Fifty-two were between 18 and 30 years of age and 27 between the latter age and 45.

The pulmonary disease was far advanced in 55 and moderately advanced in 24, according to the classification of the National Tuberculosis Association. In 63, the process was regarded as progressive, in 11 as stationary and in only 5 as regressive. The duration of their illness at the start of treatment ranged from a few months to several years.

All patients were treated for 120 days with 1.8 g. of streptomycin a day or, in a few instances, 2.0 g.

ROENTGENOGRAPHIC OBSERVATIONS

Marked clearing of exudative lesions occurred in 39 patients (49 per cent), its extent being greater than would have been anticipated as a result of bed-rest in the same length of time. In 29 additional patients (37 per cent), moderate clearing occurred, of the order that might have been expected on bed-rest, although a majority of this group had been showing progression of their disease during the pre-treatment observation period. The remaining 11 patients (14 per cent) either showed no change or, in 9 instances, an extension of their disease after a period of improvement during the first two months of therapy. Among the possible reasons for the relative failure of streptomycin treatment in this last group are an overwhelming infection, the preponderance of productive elements in the lesion and perhaps, after ninety days of treatment, an organism which had become resistant to the concentrations of streptomycin that were present in the body.

Because of the many variable factors involved in body defense against tubercu-

¹ From Fitzsimons General Hospital, Denver, Colorado.

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³ First Lieutenant, S.A.C., A.U.S.

⁴ Captain, M.C., A.U.S.

⁵ Lieutenant Colonel, M.C., A.U.S.

losis, it was considered impractical to carry on control studies in humans as one might do in laboratory experiments. Hence these results are evaluated solely on the basis of experience in treating similar cases before the advent of streptomycin.

Sixty-one cavities were visible on X-ray films of the lungs of these patients prior to initiating streptomycin therapy. Fifteen of them either closed or became lost to view during 120 days of treatment, 31 decreased in size and 15 were either unchanged or larger.

Twenty-five of these patients were lost from the series by transfer to other hospitals following the completion of treatment, but roentgenographic observations on the remaining 54 have been continued over a period which averages 150 days. Twenty-one cases (40 per cent) have shown continued improvement, 22 (40 per cent) have remained unchanged and an extension of disease has occurred in 11 (20 per cent). If larger experience confirms this finding of a progression of infection relatively soon after the termination of streptomycin therapy, it will be an important point in determining the precise rôle of this treatment.

TABLE 1
Changes in the clinical picture

	NUMBER OF PATIENTS	
	BEFORE	AFTER
Elevated sedimentation rate.....	62	42
Hemoptysis.....	17	8
Underweight in excess of 10 pounds.....	51	36
Severe cough.....	32	6
Copious sputum.....	30	5
Chills and/or sweats.....	14	3
Definitely febrile.....	50	27
Sputa more often positive than negative.....	46	25
Sputa more often negative than positive.....	7	25

CLINICAL OBSERVATIONS

Table 1 summarizes the changes in the clinical picture of our patients which were observed to occur during the 120 days of treatment. It shows a rather definite improvement. The improvement is usually noted promptly, a large part of it occurring within the first two months. It is evident that the more manifest symptoms, such as hemoptysis, severe cough, copious sputum, chills and sweats, and high fever, are lessened considerably. There is some tendency towards the conversion of sputum from positive to negative.

A definite increase in weight occurred in 69 patients and averaged 8.5 pounds. The average daily amount of sputum in 52 patients decreased from 60 to 30 cc. Temperature decreased in 23 of the 50 patients who were febrile at the time treatment was started and became normal in 19.

Toxemia: The incidence of toxemic manifestations in this series, summarized in table 2, are well in agreement with the findings of other workers with strepto-

mycin. Attention was called very early by investigators at the Mayo Clinic to the high incidence of damage to the vestibular apparatus. Recently this phenomenon, and especially the possibility of its permanency, has again come very much to the forefront because of its medico-legal aspects. Certainly, when advising the use of streptomycin in a given patient, one should weigh very carefully the clinical improvement to be expected against the potential and perhaps permanent damage to the vestibular apparatus.

The development of dermatitis in nurses working with streptomycin has created a problem which we have not yet entirely overcome. It is our present opinion that most nurses, if exposed to sufficient concentrations over a prolonged period of time, will become sensitive to streptomycin. The occurrence of aplastic anemia in patients receiving streptomycin deserves mention. Although it did not occur in the group under present discussion, 2 of our patients being treated

TABLE 2
Toxemic manifestations

	NUMBER OF PATIENTS
Vestibular disturbance (total).....	70
Severe.....	20
Romberg sign positive.....	29
Persistent vestibular disturbance up to three months after treatment:	
Of patients with positive Romberg.....	21
Of patients without positive Romberg.....	6
Eosinophilia (5 to 33 per cent).....	56
Urinary casts.....	50
Tinnitus.....	39
Nausea and vomiting.....	4
Exfoliative dermatitis.....	1
Jaundice.....	2

for pulmonary tuberculosis developed an aplastic anemia on about the ninetieth day of therapy. Neither presented evidence of hematogenous dissemination. The drug was stopped immediately. One case terminated fatally and recovery in the other is doubtful. We hesitate to name streptomycin as the offending agent, but certainly this dyscrasia occurred during streptomycin therapy. Prior to the onset of the anemia, one patient had occasionally received seconal; the other had received very small amounts of benadryl. The only other serious reaction occurred in a young white male who developed an urticarial rash about the fourth week of treatment. The drug was stopped, recovery was prompt, and the drug was restarted after a week's interruption. Three weeks later he developed a severe exfoliative dermatitis with a septic type of temperature. For this reason the drug was stopped and it has not been used again.

BACTERIOLOGICAL STUDIES

There are, at the present time, very pertinent and inviting questions relative to the *in vivo* and *in vivo* development of streptomycin resistance by tubercle

bacilli. Generally speaking, there appears to be some correlation between further clinical improvement, or lack of such improvement, and the *in vitro* resistance of the organism. Six patients whose tuberculosis progressed after the initial four months' course of streptomycin, and whose organisms were resistant to streptomycin *in vitro*, have been again placed on streptomycin with no evidence of further benefit from the drug.

An attempt was made to define some of the limitations of streptomycin through a study of its effect *in vitro* on the tubercle bacilli isolated from these patients. The following factors were investigated: (1) the initial streptomycin sensitivity of the organisms; (2) the percentage of patients who develop streptomycin-resistant tubercle bacilli during treatment; (3) the approximate period during therapy at which resistance becomes manifest; (4) the permanence or duration of this resistance.

The *in vitro* action of streptomycin was determined by the method outlined by Doctor Youmans⁶ of Northwestern University. Strains capable of growth in 10 or more micrograms streptomycin per ml. were classed as "resistant."

Initial sensitivity: A total of 110 strains of tubercle bacilli were isolated from patients never exposed to streptomycin. All strains were inhibited by 1 mcg. streptomycin per ml. of test medium.

Patients yielding resistant strains: Twenty-nine patients were checked for this phenomenon. Of these, 22 (75 per cent) yielded streptomycin-resistant tubercle bacilli after seventy to ninety days of treatment. Seven patients (25 per cent) had tubercle bacilli, isolated throughout the entire 120 days of treatment, that were streptomycin-sensitive.

Permanence of resistance: There was no apparent decrease in the extent of streptomycin resistance in tubercle bacilli maintained *in vitro* after nine months, and patients with resistant strains continued to expectorate such strains until the present writing, or ten months after the discontinuation of treatment.

Table 3 is a composite picture of the clinical course as compared with a bacteriological study of sensitivity-resistance in 22 patients.

DISCUSSION

There is need for the study of the effect, if any, which streptomycin has on the development or lack of development of the natural body resistance to this disease. It is possible that streptomycin delays or inhibits the development of the individual's natural body resistance. Because of this possibility, it is the policy in this Hospital at the present time not to use streptomycin in minimal cases where it is thought that the patient can handle the disease adequately.

One of the patients who developed streptomycin-resistant tubercle bacilli at the end of four months of streptomycin treatment showed progression during the following two months, and was again placed on streptomycin. This individual continued to progress with wide open bilateral cavities. He became discouraged and went AWOL. When such a patient is at large, with a streptomycin-resistant

⁶ G. P. Youmans: Personal communication.

strain of tubercle bacilli, it is quite possible that he will spread a streptomycin-resistant type of the disease.

TABLE 3

A comparison of streptomycin resistance and clinical response in 22 patients

PATIENTS	SEDIMENTATION RATE CUTLER		FEVER		STREPTOMYCIN OF DEFINITE VALUE	ACID-FAST BACILLI IN SPUTUM		FOLLOW-UP TO 4 MONTHS	SENSITIVITY AFTER 4 MONTHS 'YOU-MANS' MEDIUM
	Before	After	Before	After		Before	After		
AA	30	30	Febrile	Febrile	Yes	xx ¹	xx	Prog. ⁴	R ⁷
EF	29	23	Afebrile	Afebrile	Yes	xx	xx	Prog.	R
OB	10	15	Febrile	Afebrile	No	xx	xx	Sta. ⁵	S ⁸
EC	6	4	Febrile	Afebrile	No	xx	xx	Impr. ⁶	S
BC	24	7	Febrile	Febrile	Yes	xx	xx	Prog.	R
RC	23	10	Febrile	Afebrile	Yes	xx	x	Sta.	R
WD	25	5	Febrile	Afebrile	Yes	xx	xx	Prog.	S
GH	27	10	Afebrile	Afebrile	Yes	x ²	— ³	Sta.	S
CL	13	22	Febrile	Febrile	No	xx	xx	Prog.	R
JM	24	26	Febrile	Febrile	Yes	xx	xx	Prog.	R
DN	20	7	Febrile	Febrile	No	xx	x	Prog.	S
GP	17	6	Febrile	Afebrile	Yes	xx	xx	Sta.	R
TR	29	21	Febrile	Afebrile	Yes	xx	xx	Prog.	R
HR	24	27	Febrile	Afebrile	Yes	xx	xx	Impr.	S
ES	2	10	Afebrile	Afebrile	No	xx	xx	Sta.	R
GS	20	10	Afebrile	Febrile	No	xx	xx	Sta.	R
DS	23	10	Febrile	Afebrile	Yes	xx	x	Sta.	R
OW	9	5	Afebrile	Afebrile	Yes	xx	x	Sta.	S
IW	23	6	Febrile	Febrile	Yes	xx	xx	Prog.	R
HW	22	7	Afebrile	Afebrile	No	x	—	Sta.	S
RR	18	3	Febrile	Afebrile	Yes	xx	x	Sta.	S
HZ	6	12	Afebrile	Afebrile	No	xx	x	Sta.	R

¹xx = Consistently positive.

²x = Occasionally positive.

³— = Negative.

⁴Prog. = Definite disease progression.

⁵Sta. = Stationary.

⁶Impr. = Continued improvement.

⁷R = Grows in 10 U/cc.

⁸S = 10 U/cc. inhibit.

SUMMARY

Some results are presented in 79 patients with pulmonary tuberculosis treated with streptomycin and bed-rest only. It has been shown that streptomycin has altered the usual course of the disease in a majority of the cases.

Streptomycin-resistant tubercle bacilli appeared in 75 per cent of patients who had positive sputa throughout therapy. The development of such resistance may be a permanent characteristic.

SUMARIO

La Estreptomicina y el Encamamiento en el Tratamiento de la Tuberculosis Pulmonar

Al presentar 79 enfermos de tuberculosis pulmonar tratados exclusivamente con estreptomicina y reposo en cama, muéstrase que la estreptomicina alteró la evolución habitual de la enfermedad en la mayoría.

En 75 por ciento de los enfermos estudiados aparecieron bacilos tuberculosos estreptomicinorresistentes. El desarrollo de dicha resistencia puede constituir una característica permanente.

STREPTOMYCIN IN THE TREATMENT OF PULMONARY TUBERCULOSIS^{1,2}

Report of 15 Patients

ARNOLD SHAMASKIN,³ LOUIS C. MORRIS,⁴ EUGENE J. DES AUTELS,⁵ JOSEPH MINDLIN,⁶ JAMES R. ZVETINA⁶ AND HENRY C. SWEANY⁷

Sixty-four patients with a variety of tuberculous lesions have been treated by the Hines Streptomycin Study Unit since it was activated in September 1946. The present report concerns itself only with the treatment of 15 cases of pulmonary tuberculosis, and with certain extrapulmonary complications which these patients chanced to exhibit. The effect of streptomycin upon these complications, at first an accidental observation, has been most impressive and, by leading us to the treatment of similar lesions in other individuals, has become a major by-product of our study.

All 15 patients were observed for at least sixty days prior to the initiation of streptomycin therapy; they received 1.8 g. of streptomycin daily for 120 days; they have been observed for at least sixty, and for an average of 111 days following the completion of treatment. During this entire period, their regimen was altered in no other way than by the administration of streptomycin.

CLINICAL MATERIAL

Despite the fact that there were 400 tuberculous patients on our wards, we experienced great, and unexpected, difficulty in selecting cases that complied with the terms of the protocol which governed this coöperative study. The difficulty stemmed largely from the marked predominance of productive lesions among our patients and the early use of collapse therapy in those patients who were already in residence at the time our investigation was started. It required almost three months before 15 suitable cases could be collected and their treatment could be initiated.

All 15 cases were males of whom 10 were white and 5 colored. Fourteen were between 20 and 30 and one was 50 years of age. In addition to their pulmonary lesions, at which treatment was primarily directed, there were 6 extrapulmonary tuberculous lesions: 2 adenitis, one laryngitis, one enteritis, one otitis media and one pleuro-cutaneous fistula.

Of the 15 cases (table 1), 14 had far advanced pulmonary lesions and one had

¹ From the Tuberculosis Service, Veterans Administration Hospital, Hines, Illinois.

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³ Chief, Tuberculosis Service.

⁴ Attending Physician in Tuberculosis.

⁵ Assistant Chief, Tuberculosis Service.

⁶ Physician, Streptomycin Research Section.

⁷ Senior Consultant in Tuberculosis.

a moderately advanced lesion. Bilateral lesions were present in 13 cases and cavities in 13. While the patients were at bed-rest during the pre-treatment observation period, the lesions were progressive in 8, stationary in 4, and retrogressive in 3 cases.

The patients were placed on streptomycin treatment in small groups between September 28, 1946 and December 21, 1946. All cases received 0.3 g. intramuscularly every four hours for 120 days. One patient (#4) received an additional thirty days of treatment.

CLINICAL OBSERVATIONS

Lessening of cough and expectoration, improvement of appetite and gain in weight usually became evident at the end of the first week of therapy. Cough decreased within a week and was markedly diminished within a month in all but one patient (#11). Exacerbation of cough occurred in one case (#3) during the second half of treatment. Thus, 13 of the 15 cases (87 per cent) had sustained relief from cough.

With the exception of 2 patients (#5 and #11), the amount of sputum began to diminish within one week and was definitely diminished within one month of beginning treatment (table 1 and chart 1). One patient (#5) had only scanty amounts of sputum throughout the study period. Another patient (#11) raised 120 cc. per day before therapy and during the therapy period, and expectoration increased to 240 cc. per day during the after-treatment observation period. Before therapy, the remaining 13 patients raised a combined total of 1,860 cc. per day, at the end of therapy, a total of 480 cc. per day, and at the end of the after-treatment observation period, 300 cc. per day. Before therapy, 4 patients (#1, #3, #9 and #13) raised 240 cc., 240 cc., 480 cc. and 360 cc. per day, respectively; at the end of the after-treatment observation period, they raised 30 cc., 60 cc., 60 cc. and 60 cc., respectively. Thus, a marked reduction in sputum persisted in 13 (93 per cent) of the 14 patients who had measurable amounts prior to therapy.

All patients gained weight during the treatment and after-treatment periods (table 1 and chart 1), in amounts ranging from 2 to 47 pounds, with an average of 17.5 pounds per patient. Eleven patients (73 per cent) gained in excess of 8 pounds.

Before therapy, the temperature was between 100° and 103°F. in 8 cases; 99° in 4 and normal in 3 (table 1 and chart 1). After treatment, the temperature was below 99.4°F. in 12 cases (normal in 5, 99° in 5, 99.2° in one and 99.4°F. in one), and above 100°F. in 3. Of these 3 cases, 2 (#3 and #11) had an initial decline and one (#10) maintained an elevation of 100°F. throughout. Marked reduction of temperature occurred and persisted in 5 (63 per cent) of the 8 cases with elevations of 100° to 103°F. before therapy.

Streaking occurred in 7 patients (47 per cent) during streptomycin therapy. In none of them was streaking observed before treatment. This did not recur in the post-therapy period, except in one patient (#3) who had a series of severe hemoptyses two and one-half months after cessation of therapy.

TABLE 1
Clinical, laboratory and X-ray findings in 15 patients with pulmonary tuberculosis, before, during and after streptomycin therapy

CASE, RACE, AGE	CLINICAL DATA				LABORATORY DATA				X-RAY FINDINGS		
	Before	During	After			Before	During	After	Before	During	After
#1 E. H. G. W 20	Weight* Temp.** Cond. Course:	+14% 99° Fair Retrogr.	+10% 98.9° Good Retrogr.	+13% 98.6° Good Sta'y	Sput. cc. Bacilli Sed. R. Eosino.	240 Pos. 28 3	30 Pos. 20 8	30 Pos. 8 2	Exudative extensive bilateral cavitation. Retrogr.	Mkd. clear. Smaller, harder. Cav. closed.	Unchanged.
#2 W. B. M. W 50	Weight Temp. Cond. Course:	+3% 99° Fair Sta'y	+4% 99.4° Good Retrogr.	+4% 99.4° Good Sta'y	Sput. cc. Bacilli Sed. R. Eosino.	30 Pos. 25 4	Scant Pos. 18 8	15 Pos. 12 0	Pred. exud. upper third, bilateral. Cav. 1 x 1 cm. Progr.	R. unchanged. L. smaller, harder.	L. cav. 2 x 2 cm., other- wise unchanged.
#3 R. J. O. W 26	Weight Temp. Cond. Course:	-17% 103° Fair Progr.	+17% 1st decr. then incr. Fair Retrogr.	-15% 103° Poor Progr.	Sput. cc. Bacilli Sed. R. Eosino.	240 Pos. 32 0	30 Pos. 15 7	60 Pos. 28 3	R. exudative exten- sive. L. slight, with sm. cav. Progr.	Smaller, harder bilat- erally. Retrogr.	R. larger, softer. Cav. larger. L. harder.
#4 H. P. W 27	Weight Temp. Cond. Course:	+3% 101° Fair Retrogr.	+7% 99.4° Good Retrogr.	+5% 99° Good Retrogr.	Sput. cc. Bacilli Sed. R. Eosino.	90 Pos. 25 1	Scant Pos. 9 6	30 Pos. 11 2	Exudative extensive bilateral. Cav. bi- lat. Retrogr.	Mkd. clear. Smaller, harder. Cav. small- er. Retrogr.	Smaller, harder. Cav. smaller.
#5 A. C. H. C 24	Weight Temp. Cond. Course:	Sta'y 99° Good Sta'y	+13% 98.6° Good Retrogr.	+4% 98.6° Good Retrogr.	Sput. Bacilli Sed. R. Eosino.	Scant Pos. 20 3	Scant Pos. 20 0	Scant Pos. 4 0	R. exudative upper half, sl. effusion. Progr.	R. mkd. clear. Small- er, harder. Effu'sn increased. Retrogr.	Parenchymal un- changed. Effusion absorbed.
#6 D. E. K. W 22	Weight Temp. Cond. Course:	-5% 100° Poor Progr.	+20% 99° Good Retrogr.	+3% 99° Good Sta'y	Sput. cc. Bacilli Sed. R. Eosino.	90 Pos. 26 0	30 Pos. 10 1	30 Pos. 23 0	Exudative extensiv. bilateral cavitation. Sta'y	Smaller, harder. Cav. smaller. Retrogr.	R. cav. smaller. L. larger, softer, cav. same.
#7 W. A. M. W 25	Weight Temp. Cond. Course:	-3% 98.6° Poor Progr.	+36% 99° Good Retrogr.	+11% 98.6° Good Retrogr.	Sput. cc. Bacilli Sed. R. Eosino.	90 Pos. 29 0	30 Pos. 0 17	Scant Pos. 0 5	L. exudative upper half. Cav. 3 x 3 cm. Progr.	Mkd. clear. Smaller, harder. Cav. closed. Retrogr.	Nearly disappeared, harder. Cav. closed.

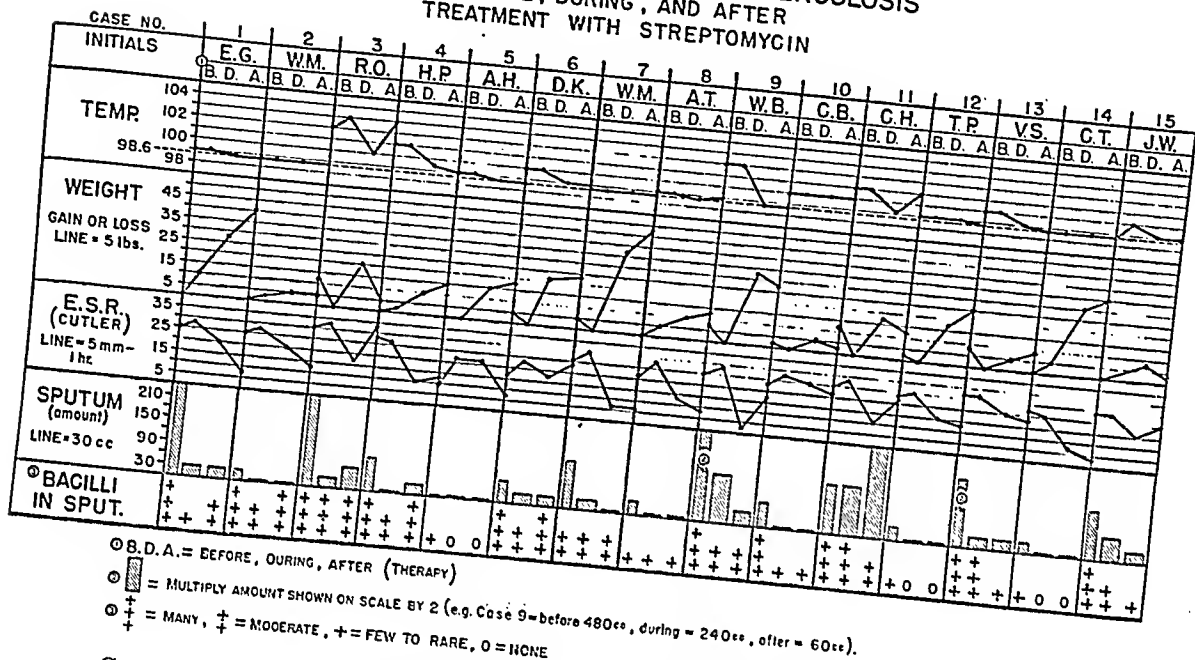
#	Weight Temp. Cond.	+4# 99° Good	+0# 99° Good	+2# 99° Good	Sput. ec. Bacilli Sed. R. Eosino.	30 Pos. 4	Scant Pos. 15 7	Scant Pos. 8 1	L. exudativo upper half. Cav. 3 x 3 cm.	Smaller, harder. Cav. lost to view.	Smaller, harder. Cav. 3 x 2 cm.
#8 A. H. T. C 29	Course:	Sta'y	Retrogr.	Retrogr.					Sta'y	Retrogr.	Retrogr.
#9 W. B. C 27	Weight Temp. Cond.	-0# 102° Fair	+31# 99° Good	-2# 99° Good	Sput. ec. Bacilli Sed. R. Eosino.	480 Pos. 26 0	240 Pos. 2 17	60 Pos. 17 0	Exudativo extensivo bilateral. Cav. 11 x 8 cm.	Mkd. clear. Smaller, harder. Cav. 8 x 6 cm.	Smaller, harder. Cav. 10 x 7 cm.
#10 C. A. B. W 33	Course:	Progr.	Retrogr.	Retrogr.					Progr.	Retrogr.	Retrogr.
#11 C. H. C 22	Weight Temp. Cond.	-2# 100° Fair	+5# 100° Good	-3# 100° Fair	Sput. ec. Bacilli Sed. R. Eosino.	60 Pos. 26 3	Scant Pos. 25 20	Scant Pos. 21 0	Exudativo extensivo bilateral. Cav. 5 x 8 cm.	Unchanged.	Larger, softer. Cav. 0 x 5 cm.
#12 T. A. P. W 22	Course:	Progr.	Retrogr.	Progr.					Progr.	Sta'y	Progr.
#13 V. S. W 25	Weight Temp. Cond.	-8# 101° Fair	+17# 99.4° Good	-0# 101° Fair	Sput. ec. Bacilli Sed. R. Eosino.	120 Pos. 27 1	120 Pos. 10 20	240 Pos. 22 1	Exudativo extensivo bilateral. Cavitation.	Mkd. clear. Smaller, harder. Cav. samo.	Smaller, harder. Cav. larger.
#14 C. T. W 25	Course:	Sta'y	Retrogr.	Retrogr.					Progr.	Retrogr.	Sta'y
#15 J. W. C 22	Weight Temp. Cond.	-2# 100° Fair	+7# 99.4° Good	-5# 99.2° Good	Sput. ec. Bacilli Sed. R. Eosino.	120 Pos. 24 1	60 Pos. 15 16	20 Pos. 20 7	Exudativo extensivo bilateral. Cav. 6 x 5 cm.	Smaller, harder. Cav. 5 x 4 cm.	Unchanged. Cav. 5 x 4 cm.
#16 C. T. W 25	Course:	Progr.	Retrogr.	Retrogr.					Progr.	Retrogr.	Sta'y
#17 V. S. W 25	Weight Temp. Cond.	-0# 100° Poor	+5# 99° Good	+4# 99° Good	Sput. ec. Bacilli Sed. R. Eosino.	300 Pos. 27 0	300 Pos. 27 14	60 Pos. 19 2	Exudativo extensivo bilateral cavitation.	Mkd. clear. Smaller, harder. Cav. smaller.	Smaller, harder bilat- erally. Cav. larger.
#18 C. T. W 25	Course:	Progr.	Retrogr.	Retrogr.					Progr.	Retrogr.	Retrogr.
#19 J. W. C 22	Weight Temp. Cond.	-2# 100° Fair	+7# 99.4° Good	-5# 99.2° Good	Sput. ec. Bacilli Sed. R. Eosino.	120 Pos. 24 1	60 Pos. 15 16	20 Pos. 20 7	Exudativo extensivo bilateral. Cav. 6 x 5 cm.	Smaller, harder. Cav. 5 x 4 cm.	Unchanged. Cav. 5 x 4 cm.
#20 C. T. W 25	Course:	Progr.	Retrogr.	Retrogr.					Progr.	Retrogr.	Sta'y

* Throughout table + or - represents gain or loss of weight during the specific period indicated.

** Temperatures recorded were the average daily high.

A relapse of symptoms occurred in one patient (*3) during the second half of treatment, and progression has continued in the after-treatment period. During the after-treatment period, exacerbation of symptoms occurred in another patient (*11); 10 patients continued to improve and 3 remained stationary. General

SUMMARY OF CLINICAL COURSE OF 15 CASES OF PULMONARY TUBERCULOSIS BEFORE, DURING, AND AFTER TREATMENT WITH STREPTOMYCIN



(ONLY 24HR. CONCENTRATED SPUTA EXAMINED)

CHART 1. Shows at a glance the striking effect of streptomycin on the clinical course of exudative and progressive pulmonary tuberculosis.

It may be noted that, during the period of streptomycin therapy, the general trend of the temperature was down in every case where it was previously elevated, except in one (C.B.). In this case the temperature remained unchanged at 100°F. and, significantly, the weight and the sedimentation rate show a corresponding lack of material change. There was a weight gain in every case and a drop in sedimentation rate in every case except 2, including the one previously mentioned.

The reduction in amount of sputum and its bacillary content is discussed elsewhere. The direction of the weight and sedimentation rate curves is obviously of prognostic significance. Usually when the lines diverge the patient's improvement continues and, when they begin to converge, progression of the disease takes place. Thus, one can see at a glance the trend of the disease in each case during the three periods of study illustrated.

symptomatic improvement was thus maintained in 13 (87 per cent) of the original 15 cases.

ROENTGENOGRAPHIC OBSERVATIONS

X-ray interpretations of the pulmonary lesions before therapy (table 1) were recorded as progressive in 8, stationary in 4 and retrogressive in 3 patients.

During therapy, 14 cases were recorded (table 1) as retrogressive and one as stationary. During the post-therapy period the interpretations (table 1) were recorded as continued retrogression in 8 (53 per cent), stationary in 4 (27 per cent) and progressive in 3 cases (20 per cent).

Radiological evidence of clearing and hardening of exudative lesions was evident in all cases after one to two months of treatment. Cavities were lost to view in 3 (23 per cent) (#1, #7 and #12) of the 13 patients who showed cavitation prior to therapy and became smaller in one (#4).

LABORATORY OBSERVATIONS

The bacillary content of the sputum (chart 1) showed a tendency toward reduction but this was not as clearly defined as other features of improvement. The sputum of all patients (chart 1) contained tubercle bacilli prior to therapy. No tubercle bacilli were demonstrated in the sputum or gastric contents of 3 patients (20 per cent) following therapy. This did not include examinations by culture or guinea pig inoculation for the reason given in a subsequent section of this report.

The sedimentation rates ranged from 20 to 32 mm. per hour in all cases prior to therapy (table 1). A decline of more than 15 mm. per hour occurred in 11 cases (reaching 2 to 10 mm. per hour in 9) and a slight decline in 4 (#6, #10, #13 and #15). Considerable elevation of sedimentation rate recurred in 3 cases (#3, #9 and #11). Thus, 8 patients (53 per cent) ended the study periods with significant reduction in sedimentation rates.

There was no significant change in the erythrocyte or hemoglobin determinations during the study periods.

The leucocyte and differential counts revealed that cases with higher counts showed a tendency to become lower. There was also a tendency toward relative lymphocytosis in most of our patients near the end of the therapy period. Only one case (#14) revealed persistent eosinophilia of from 5 to 50 per cent during therapy, although it was periodically present in 12 of the other 14 patients. This patient had no other definite evidence of toxemia or allergic reactions. The eosinophil count recorded in table 1 is merely the single highest count, out of an average of 17 determinations per patient.

Four patients developed slight albuminuria (table 2) during therapy and this persisted in one (#7). Casts were found in 2 cases (#12 and #13) during treatment only.

Renal function, as determined by nonprotein nitrogen and urea clearance tests, remained normal in all patients throughout the study.

Bromsulphalein liver function tests revealed retention of 15 to 25 per cent in 4 of the 15 cases before therapy, but all cases revealed normal tests at the end of treatment.

Blood streptomycin levels were determined on an average of five times per patient. Representative values, four hours following an injection (usually at 10 a.m.), were 12 to 21 mcg. per cc. of blood serum and averaged 16 mcg. per cc.

The results of our efforts to examine the development of resistance to strepto-

OBSERVATIONS ON EXTRAPULMONARY LESIONS

Tuberculous otitis media occurred in one case (§9). Aural drainage ceased in about two weeks and did not recur.

One patient (§6) had clinical evidences strongly suggestive of intestinal tuberculosis supported by X-ray evidence of a filling defect and hyperperistalsis. He had marked abdominal cramps and three to five loose stools per day over a period of ten months. All the symptoms disappeared within two weeks from the beginning of treatment and have not recurred to date. There was no significant change in the intestinal X-ray film.

A patient with an extensive laryngeal lesion experienced prompt improvement of symptoms, and marked healing was observed on subsequent laryngoscopic observations.

Two patients (§5 and §15) had plum-sized tuberculous cervical lymph nodes for about four months prior to therapy. In both patients the nodes shrank to about peanut-size during therapy. Since termination of treatment, the enlarged nodes disappeared in one patient (§5) and remained unchanged in one (§15).

TOXICITY OF STREPTOMYCIN

Three instances of transient, and one of persistent albuminuria have already been commented upon, as has the occurrence of eosinophilia in 13 of the 15 patients. The only other minor evidences of toxicity (table 2) have been the occurrence of nausea and vomiting in one instance, a slight skin eruption in another and pruritus in 2.

More serious are the manifestations of interference with vestibular function which occurred, in greater or lesser degree, in 12 of our 15 patients (table 2). Nor, unfortunately, is this manifestation peculiar to our experience, for it was present in 96 per cent of some 800 cases recently reported upon (1). In our series, these symptoms appeared usually within one month or one month and a half from the beginning of treatment. They usually lasted about three to four weeks and gradually subsided as the patient learned to compensate for this impairment. Some of our patients had moderate to severe vertigo periodically throughout the period of treatment and even for a few weeks after its completion. It was noted that, as a rule, the vestibular symptoms came on earliest, were most severe and lasted longest in the older age group, confirming the observations of other investigators (1).

The incidence of normal responses to caloric stimulation in our cases is higher than would be anticipated from the incidence of vestibular symptoms. In 3 cases (§1, §4 and §3) the normal responses coincide, as one would expect, with a total absence of clinical manifestations suggestive of vestibular dysfunction at any time during the course of treatment. We are at a loss, however, to explain the normal caloric response in the presence of symptoms of vestibular dysfunction in 6 other cases (§3, §8, §9, §11, §13 and §15). This is at variance with observations made by other investigators (1).

It is to be feared that this effect upon the vestibular function is due to the streptomycin itself rather than to impurities in the preparation as had, earlier, been hoped. Recent studies (2) indicate that the effect is upon vestibular nuclei

TABLE 2
Toxic reactions to streptomycin

CASE NUMBER	VESTIBULAR MANIFESTATIONS					EOSINOPHILIA, HIGHEST PER CENT DURING TREATMENT	OTHERS
	Symptoms				Vestibular Function Caloric Test		
	Vertigo*	Unsteady gait*	Tinnitus*	Blurring of vision*			
1 E. H. G.	0	0	0	0	Normal	8	0
2 W. B. M.	+++	+++	0	+	Marked impairment	8	0
3 R. J. O.	+++	+++	+++	0	Normal	7	Nausea and vomiting
4 H. P.	0	0	0	0	Normal	6	Slight skin rash
5 A. C. H.	0	0	0	0	Normal	5	0
6 D. E. K.	+++	+++	+	+	Marked impairment	7	Frontal headaches
7 W. A. M.	++	+	0	0	Mod. impairment	17	Persistent albuminuria
8 A. H. T.	+	+	0	0	Normal	7	0
9 W. B.	+	+	0	+	Normal	17	Albuminuria, transitory
10 C. A. B.	+	+	0	+	Mod. impairment	20	Albuminuria, transitory
11 C. H.	+	+	+	+	Normal	29	Pruritus
12 T. A. P.	++	+++	++	+	Marked impairment	8	Parasthesia and headache Cylindruria, transitory
13 V. S.	0	+	0	0	Normal	14	Transitory albuminuria and eyindruria
14 C. T.	0	+	++	0	Marked impairment	50	0
15 J. W.	0	+	0	0	Normal	16	Pruritus

* + Mild
 ++ Moderate
 +++ Severe
 0 None

Three patients developed transitory albuminuria; one of them with cylindruria. One patient developed albuminuria which has persisted since completion of treatment. In 5 patients who had albuminuria before treatment, this condition cleared up after streptomycin treatment was instituted, probably due to relief of toxemia.

in the brain rather than upon the eighth cranial nerve proper. It remains to be seen whether the employment of smaller doses than those used in the present study may mitigate or abolish this toxic manifestation of streptomycin without diminishing its therapeutic efficacy. This possibility has been the sub-

ject of active study in our Hospital, as well as in others, since May 1947. Thus far, it would seem that the incidence and severity of vestibular symptoms are less and, in certain types of tuberculosis at least, the immediate effectiveness of streptomycin is as great as with larger doses. The ultimate effectiveness of these small doses must still be proved.

None of our patients suffered any diminution in the acuity of their hearing during streptomycin therapy.

EFFECT OF STREPTOMYCIN ON THE VIABILITY OF TUBERCLE BACILLI IN SECRETIONS

Shortly after we began to culture tubercle bacilli from the sputum and gastric contents of our streptomycin-treated patients for sensitivity tests, we observed a peculiar discrepancy between the results obtained from the simultaneous examinations of secretions by smear and by culture. In the vast majority of instances, no growths were reported on culture of specimens in which tubercle bacilli were found on smear. The only explanation for this discrepancy which occurs to us is that the organisms excreted by the streptomycin-treated patients are either dead or are so devitalized that they are frequently unable to produce a visible growth on a culture medium in the usual six to eight weeks, but may take as long as six to eight months to do so. For this reason our reports on the bacillary content of sputa (table 1) are based, in many instances, on the examination of concentrated twenty-four-hour specimens by direct smear rather than by culture. A check of our past laboratory records produced no instances wherein the direct smears of sputa were more sensitive than the cultures in revealing tubercle bacilli.

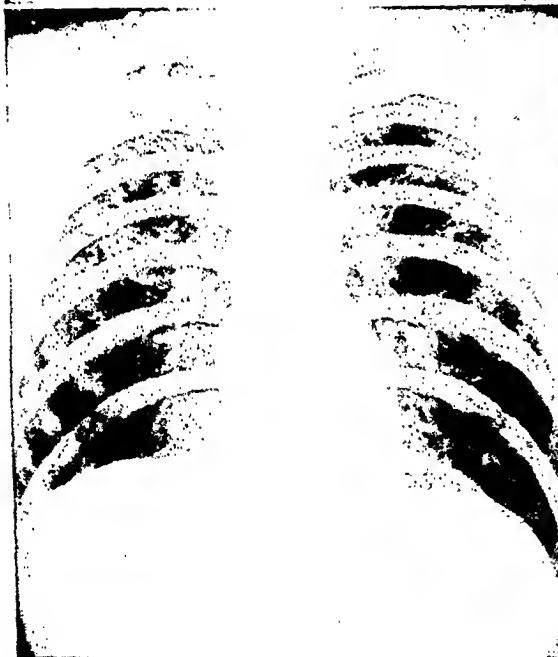
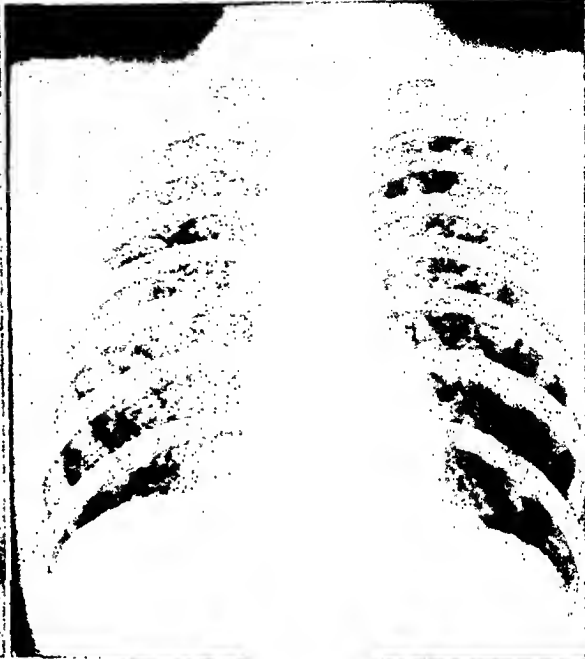
DISCUSSION

Almost complete resolution of pulmonary lesions took place in 3 (20 per cent) (#7, #12 and #14) of our 15 cases, with disappearance of cavity in 2 (#7 and #12). In addition, in a number of patients, whose condition had been too acute to permit other procedures, the lesions retrogressed sufficiently both clinically and roentgenologically, during treatment with streptomycin, to become suitable for collapse therapy. Thus, it became feasible to induce pneumothorax in 3 patients, pneumoperitoneum in 2, a phrenic crush was performed in one and thoracoplasty was recommended in another—a total of 7 out of 15, or 47 per cent of the pulmonary patients whose streptomycin treatment was completed. Case 13 is typical of this group of patients (figures 1a, b, c and d).

In reviewing our experience with streptomycin in the treatment of progressive exudative pulmonary tuberculosis, one is not so much impressed with the individual case, since the results observed in each could have taken place under rest-treatment alone—albeit rarely and less rapidly—as by the total picture of a sudden reversal in the course of disease and a profound effect on symptoms which occurred coincident with the beginning of streptomycin therapy in all patients. Although the study of pulmonary lesions was our primary concern, we were most impressed by the startling effect of streptomycin on the two common and

a

b



c

d

FIG. 1a. (*Upper left*) This roentgenogram was taken September 7, 1946, nearly three months before streptomycin therapy was started. It shows an extensive exudative involvement of both lungs from apex to base with cavitation in the middle third of the right lung. Temperature 100°F. Sedimentation rate 27.

FIG. 1b. (*Upper right*) Roentgenogram, taken November 27, 1946 immediately before streptomycin, shows further extension of the disease in the lower lobes.

FIG. 1c. (*Lower left*) Roentgenogram, taken March 26, 1947 at termination of treatment, shows marked clearing in lower lobes. Lesion appears harder and cavity smaller.

FIG. 1d. (*Lower right*) Roentgenogram taken June 5, 1947, about two months after termination of therapy, shows the lesion still smaller and harder but cavity is larger. Pneumothorax was induced on the right side June 23, 1947.

serious extrapulmonary complications which were present in our patients, laryngeal and intestinal tuberculosis.

Much, of course, remains to be learned of the optimum regimen for streptomycin therapy, of its indications and contraindications, of measures to diminish or avoid the toxemic manifestations which accompany it. But, from the evidences secured thus far by ourselves and others, it is clear that we are on the threshold of a new era in the treatment of tuberculosis. We have in streptomycin the most potent therapeutic agent thus far available, one that is capable of inhibiting the growth of the tubercle bacillus inside the human host.

Until we know more, however, about the *full* significance of the vestibular dysfunction which occurs in such a high percentage of the patients under prolonged streptomycin treatment with doses heretofore employed, as well as about other toxemic manifestations, it should be used cautiously. In the present state of our knowledge, it would seem best to confine its use, in the treatment of pulmonary tuberculosis, to patients who have exudative lesions or lesions with an exudative component, which have continued to progress or have remained stationary under rest treatment alone. Furthermore, streptomycin therapy should be carried out in a hospital equipped with adequate facilities for laboratory control as well as for accurate audiometric and caloric tests.

When considering a case of tuberculosis for streptomycin therapy, one must weigh, of course, the seriousness of the possible toxemic effects of the drug against the consequences of an uncontrolled tuberculous lesion and make one's decision accordingly.

Finally, this presentation would not be complete without a warning which cannot be emphasized too strongly and too often, that streptomycin must be looked upon as only a valuable aid to rest and collapse therapy, not as a substitute for these time-proven methods in the treatment of pulmonary tuberculosis.

SUMMARY

Fifteen cases of exudative or predominantly exudative pulmonary tuberculosis have been treated with streptomycin and studied with some care, both during their treatment and during a subsequent observation period which averaged 111 days. The following noteworthy points are brought out:

1. Definite clinical improvement occurred in all 15 patients during therapy and was maintained in 13 (83 per cent) during the after-treatment observation period. Roentgenographic improvement occurred during therapy in 12 patients whose lesions had been progressive or stationary during the control period and continued in 3 cases which had been regressive at that time. Three spreads occurred during the after-treatment observation, 8 patients continued to improve and 4 remained stationary.

2. The sudden reversal of the clinical and roentgenographic course of the disease, simultaneous with the beginning of streptomycin treatment, might be regarded as a coincidence in any single case but it occurred with such uniformity in our series as to argue strongly for a cause and effect relationship.

3. The effect of streptomycin on the few extrapulmonary complications encountered in this series was strikingly favorable.

4. It is the present belief that the toxemic manifestations, as now encountered, are probably inherent in the drug itself rather than being due to impurities.

5. The effect of streptomycin on the vestibular apparatus is the most important toxemic manifestation, not only because of the possible serious consequences of permanent damage to it, but also because it occurs in such a high percentage of cases treated over thirty days with the doses employed in this study.

6. Streptomycin must be considered only as an aid to rest and collapse therapy, not as a substitute for them.

SUMARIO

La Estreptomicina en la Tuberculosis Pulmonar: 15 Observaciones

Quince casos de tuberculosis pulmonar, bien exudativa o de predominio exudativo, fueron tratados con estreptomicina y estudiados con atención, tanto durante el tratamiento como durante un período subsiguiente de observación que promedió 111 días. Los puntos siguientes son dignos de nota:

1. En los 15 enfermos se observó mejoría clínica bien definida durante la terapéutica, manteniéndose en 13 (83 por ciento) durante el período subsiguiente de observación. En 12 enfermos cuyas lesiones habían sido evolutivas o estacionarias durante el período de anterior de observación observóse mejoría radiográfica, y ésta continuó en 3 casos que habían sido regresivos antes. Durante el período subsiguiente de observación hubo tres casos de propagación, 8 enfermos continuaron mejorando y 4 permanecieron estacionados.

2. El súbito viraje de la evolución clínica y radiográfica, que fué simultáneo con la iniciación de la estreptomicinoterapia, podría ser considerado como coincidencia en un caso aislado, pero se presentó con tanta regularidad en esta serie que aboga poderosamente en pro de una relación de causa y efecto.

3. El efecto de la estreptomicina sobre las pocas complicaciones extrapulmonares observadas fué notable por lo favorable.

4. La opinión actual es que las manifestaciones toxémicas, observadas hoy día, derívanse probablemente de la droga misma más bien que de la presencia de impurezas.

5. El efecto de la estreptomicina sobre el aparato vestibular constituye la más importante manifestación toxémica, no sólo debido a las posibles consecuencias graves de una lesión permanente del mismo, sino también por afectar a un porcentaje tan elevado de los casos tratados más de 30 días con las dosis empleadas en este estudio.

6. La estreptomicina debe ser considerada como un coadyuvante del reposo y de la colapsoterapia, y no como sustituto de los mismos.

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PULMONARY TUBERCULOSIS TREATED WITH STREPTOMYCIN^{1,2}

A Report of 20 Patients

W. A. CASSIDY³ AND EDWARD DUNNER⁴

The Veterans Administration Hospital, Livermore, California, joined the group of Federal hospitals studying the effects of streptomycin in the treatment of pulmonary tuberculosis in July 1946. This report will describe the results of treatment in 20 patients who received streptomycin for 120 days between October 1946 and February 1947, and who were observed for an average of ninety-nine days thereafter.

CLINICAL MATERIAL

All 20 patients were observed in this Hospital for at least three months prior to the commencement of streptomycin therapy. Prior to this period of observation, 13 of the 20 had received some type of collapse therapy but in only 2 was it still in effect at the beginning of the period: one pneumothorax on the contralateral side from the lesion selected for treatment, and one temporary diaphragmatic paralysis. In these 2 cases, the degree of collapse was maintained at approximately the same level during the succeeding ten months of pre-treatment, treatment and after-treatment observation.

All patients were males, 16 being white (including 3 Mexicans), 3 Negroes and one American Indian. Thirteen were under 30 years of age and 7 between 30 and 41.

Fifteen patients had far advanced and 5 moderately advanced disease according to the Diagnostic Standards of the National Tuberculosis Association. The pulmonary lesions, in all 20, were regarded as having a predominantly exudative character. In 10, the disease was both clinically and roentgenographically progressive and in 10 it had been stationary on bed-rest. Twelve patients had cavities, unilateral in most, bilateral in some, varying in size from a few millimeters to 4.0 cm. in diameter except for 4 "tension" cavities with fluid levels, the largest of which was 5.5 x 8.5 cm.

Sputum examinations in all cases were positive for acid-fast bacilli by examination of smears, and all were subsequently confirmed by culture. The tuberculin test was positive in all.

REGIMEN

The terms of the protocol covering the study were adhered to, all patients receiving 1.8 g. of streptomycin daily for 120 days (in one case, 150 days). No

¹ From the Department of Medicine and Surgery, Veterans Administration Hospital, Livermore, California.

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³ Clinical Director.

⁴ Chief of Tuberculosis Service.

patient refused a single injection and none, once placed under treatment, was dropped from the series.

RESPONSE TO TREATMENT

Roentgenographic Observations

The single measurement by which the therapeutic efficacy of streptomycin in the treatment of these cases could best be measured was by the careful review of roentgenograms taken frequently during the entire pre-treatment, treatment and after-treatment period. For this reason particular attention was given to the interpretation of X-ray films. Not only did the investigators record their readings, but all films were examined by a jury of physicians, not themselves directly concerned with this study but well acquainted with the roentgenographic changes to be expected in the disease. The jurors were Drs. Chesley Bush, H. H. Jensen and J. L. Gompertz, and their interpretations of the radiological changes will be included with those of the investigators (table 1).

Cavities: Thirteen patients had 15 definite and easily recognizable cavities at the time treatment was begun. All these excavations were present during the pre-therapy period and none had become smaller during it; some were increasing in size. Six of the 15 either closed or were lost to view at the end of treatment. Of these 6, one was a large "tension" cavity with fluid level, another was a recently developed excavation in a confluent area of infiltration and the remaining 4 were of varying ages and dimensions.

Four cavities were unaffected by streptomycin; 3 of these had been present and unchanged for many months prior to treatment and closure could scarcely have been expected to occur. The fourth was the largest of the entire group, a "blocked" cavity measuring 5.5 x 8.5 cm. in diameter. In addition to its failure to decrease in size, there developed, during treatment, a new area of excavation adjacent to it.

Two cavities became larger. Both had been increasing gradually before treatment and streptomycin had no significant effect in changing this progress.

The remaining 3 cavities became smaller.

Two definite impressions were gained by both the investigators and the jury. The first was that, in general, relatively recent thin-walled cavities responded better than old, thick-walled excavations. The second impression was that, although occasionally large "tension" cavities promptly disappeared during therapy, the total results in the treatment of blocked cavities were disappointing.

Exudative lesions: Exudation, as interpreted by review of X-ray films, is frequently difficult to distinguish from other pathological changes, but there is no other clinical method by which acute inflammation of pulmonary tissue can be recognized. Consequently, what have been called exudative lesions in this series, represent the personal interpretations of the physicians reviewing the X-ray films.

Exudative lesions were significantly improved in 18 of the 20 patients. In the opinion of the jury, changes of this degree had rarely, and in one instance never,

TABLE 1
Clinical, roentgenological and laboratory data showing the effect of streptomycin
treatment on 20 patients with pulmonary tuberculosis

CASE NUMBER	AGE	RACE	EXTENT OF DISEASE PRIOR TO TREATMENT	Sputum**			X-ray changes	REMARKS
				A*	B*	C*		
1	30	W	M. A., recent spread	+	-	-	Exud. comp. cleared	—
2	33	W	F. A., recent lesion	+	-	-	Exud. comp. cleared; prol. sm.	
3	23	W	F. A., tension cav.	+	-	-	Exud. cleared; cav. sm.	TB urinary bladder cleared, urine sterile
4	41	W	F. A., cav. with fluid level, R Cav. with ext. infil., L	+	-	-	Cavs. closed; infil. mkd. sm.	
5	33	Mex.	F. A., recent cav.	+	-	-	Cav. closed; exud. mkd. cleared	—
6	22	W	M. A., recent lesion	+	-	-	Exud. mod. cleared	
7	21	C	M. S., small recent cav.	+	-	-	Cav. closed; exud. mkd. cleared	Hemoptysis 63rd day
8	40	Mex.	F. A., cav. R; infil. L	+	+	+	Cav. closed; exud. mod. cleared	
9	27	Ind.	F. A., recent spread L; prol. R	+	-	-	Cav. closed; exud. mod. cleared; prol. sm.	Hemoptysis 30th day
***10	30	C	F. A., large cav. R; ext. infil. R and L	+	+	+	Exud. mod. cleared; prol. sm.	
11	28	W	F. A., cav. L; recent spread R	+	+	+	Cav. sm.; exud. mod. cleared; prol. N.C.	—
12	38	W	F. A.	+	+	+	Cav. sm.; exud. sm.	
13	25	W	M. A., recent spread R	+	-	-	Exud. mod. cleared	—
14	23	W	F. A., bilateral cavs.	+	+	+	Exud. mod. cleared	
15	32	W	F. A., cav. L	+	-	+	Cavs. N.C.; exud. cleared	Hemoptysis 64th day
16	21	C	F. A., tension cav.	+	+	+	Cav. N.C.; exud. mod. cleared	
17	25	W	F. A., 5.5 x 8.5 cm. tension cav.	+	+	+	Cav. N.C.; prol. sm.	Sputum increased after treatment
18	24	Mex.	F. A., cav. R; clear L	+	+	+	Exud. mod. cleared; cav. N.C.; new cav. appeared	
19	24	W	F. A., cav.	+	+	+	Cav. larger; prol. sm.	Spontaneous pneumothorax 76th day
20	23	W	M. A., exud. L; pneumothorax, R, maintained	+	-	+	Cav. larger; exud. mod. cleared	
							Exud. mkd. cleared	Relapse one week after treatment stopped

*A = Before treatment.
*B = End of treatment

*C = End of observation
** = Smear and culture.

*** = 150 days' treatment.

Exud. = Exudative lesion.
Prol. = Proliferative lesion.
Infil. = Infiltration.
Cav. = Cavity.
Comp. = Completely.
Mkd. = Markedly.

Ext. = Extensive.
R = Right.
L = Left.
Mod. = Moderately.
Sm. = Smaller.
NC = No change.

been seen before; complete clearing of an entire moderately advanced tuberculous process occurred in this patient.

Complete resolution of exudative components, leaving only fibrosis or cavities, occurred in 3 of these 18 patients and more than 50 per cent regression in 3 others. One of the 2 patients who were recorded as unimproved during treatment showed moderate improvement of the exudative disease for three months, but during the last month of therapy this favorable trend did not continue and a new cavity appeared. In the second, there was no appreciable retrogression although he experienced considerable symptomatic improvement.

It should be emphasized that the tuberculous processes in all of these patients were either stationary or progressive prior to the administration of streptomycin and that these measurable changes had occurred only when streptomycin was added to their therapy.

Proliferative lesions: In contrast to the exudative lesions, proliferative and fibro-caseous disease, as interpreted from X-ray films, did not disappear in any instance. In the majority of patients (75 per cent) in whom this type of pathological change was considered to be present, the investigators and the jury felt that some part or parts of the involved areas showed improvement, in the sense that the lesions became smaller or more dense, but in no instance was this change considered to be of significant degree.

Other types: Extensive pneumonic infiltrations, large atelectatic areas and pleural effusions were not encountered in this series.

New lesions during treatment: In one instance during the 120-day treatment period, a small pleural effusion developed. This was considered to be a new lesion although its subsequent course was benign and it disappeared without an accessory therapeutic measure. In a second case, as described above, a new cavity appeared adjacent to a large excavation.

Clinical Observations

General: Within a few days of the start of therapy, all patients stated that they felt better. These statements were spontaneous and universal, and the investigators are of the opinion that they were not solely due to psychic factors. Furthermore, as treatment was continued, and despite X-ray evidence that the tuberculous processes were only slowly improving, the feeling of being "pepped up" remained, even assuming in some patients a mild euphoria.

In addition to this "tonic effect," other, more measurable, symptomatic improvement occurred.

Cough: The frequency and productiveness of coughing decreased markedly in 18 patients. Long, hacking and often painful paroxysms were frequently eliminated or reduced.

Sputum: The amount of sputum was also significantly reduced in 18 of the 20 patients. The average reduction was precisely by half, the average daily output falling from 60 to 30 cc. Its purulency was also decreased, so that expectoration became easier. In one of the remaining 2 patients, the reduction was insignificant; in the other, there was a slight increase in the daily production.

Weight: Sixteen of the 20 patients gained weight during the treatment period (table 2). Of the other 4, 2 lost 3 and 4 pounds, respectively; and 2 were unchanged. The 2 who lost weight had cavities that appeared or enlarged during treatment. Of the 16 who increased in weight, 2 gained more than 50 pounds, 2 others more than 30, and the average for the 16 was 20 pounds. This seems

TABLE 2
Clinical and laboratory results of treatment

CASE NUM- BER	AGE	RACE	SENSITIVITY OF TUBERCLE BACILLI (MCG. STREPTOMYCIN PER CC.)					SEDIMENTATION RATES**			WEIGHT (POUNDS)			TEMPERATURE (DEGREES F.)		
			Before therapy	Days of therapy			2 to 4 months after therapy	MM. PER HOUR			A*	B*	C*	A*	B*	C*
				30	80-90	120		A*	B*	C*						
1	30	W	2	—	—	—	—	8	9	5	159	160	159	N	N	N
2	33	W	1	—	8	—	—	20	14	10	152	160	163	100	N	N
3	23	W	1	4	—	—	—	25	13	12	139	160	161	102	N	N
4	41	W	3	—	10	—	—	27	21	9	94	114	122	102	N	N
5	33	Mex.	1.5	5	—	—	—	23	15	9	135	151	152	102	N	N
6	22	W	1	4	—	—	—	18	9	5	127	145	145	100	N	N
7	21	C	0.7	—	—	—	—	16	25	5	149	168	172	N	N	N
8	40	Mex.	1.5	5	10	—	—	26	17	8	154	192	209	100	N	N
9	27	Ind.	1	4	—	60	40	25	18	8	181	198	206	N	N	N
10	30	C	0.6	2	—	—	—	20	10	4	118	151	171	102	99	N
11	28	W	0.8	3	6	30	—	17	13	6	126	138	137	100	N	N
12	38	W	1	3	7	20	20	21	19	3	175	183	200	N	N	N
13	25	W	2	3	7	80	—	19	16	13	150	156	163	N	N	N
14	23	W	2	—	—	—	—	24	10	4	143	147	149	N	N	N
15	32	W	7	—	—	—	—	22	15	16	127	151	158	N	N	N
16	21	C	6	20	200	100	100	24	24	28	132	132	130	100	N	N
17	25	W	0.9	3	10	20	20	14	21	13	130	127	131	N	101	101
18	24	Mex.	3	8	10	30	20	19	11	11	196	162	166	N	N	100
19	24	W	1	3	20	160	160									
20	23	W	1.5	6	10	160	260									
			3	8	—	1,000										

A* = Before treatment.

B* = At end of treatment.

C* = End of observation period after treatment.

N = Normal.

** Cutler method.

particularly remarkable as only 2 of the group weighed less than 125 pounds when treatment was started.

Temperature: Nine patients had normal temperatures throughout the observation period (table 2). All of these remained normal. In 8 patients, daily temperatures above 100°F. became normal, usually within a week after commencing streptomycin, and in 7 cases it remained normal. The remaining 3 patients showed some reduction in temperature, but it did not become normal and the reduction was only temporary in 2 of the 3.

Laboratory Data

Sedimentation rates: Nineteen patients had elevated sedimentation rates before therapy was started (table 2). These ranged from 14 mm. (Cutler method) to 27 mm. an hour. At the end of the ninety-nine-day observation period, the rate was below 10 mm. per hour in 11. In 6 patients the rate was unchanged or but little reduced. These reductions, initiated during therapy, showed further slowing immediately following its termination. In 2, it increased 3 to 4 mm. an hour. In one of these 2, a cavity had become larger and the other had developed a new excavation; both had lost weight and had minimal reduction of fever.

Sputum conversion: The sputum of each patient was positive for tubercle bacilli by direct examination during the pre-treatment period, and this finding was confirmed by culture. At the end of the 120 days' therapy, 11 patients (55 per cent) had negative sputum, both by direct examination and culture of the sputa or gastric contents (table 1). It had remained negative by the same methods in 10 of the 11 patients during the ninety-nine days of the post-therapy period. Another patient's sputum was converted in the post-therapy period. The total conversion rate was therefore 55 per cent with but one relapse.

The Gaffky count was reduced to lower numbers in all of those whose sputum was not converted.

Conversion occurred within the first month in 3 patients, during the second month in 3 others and between the second and fourth months in the remaining 4. Without exception, the conversion occurred in those patients whose X-ray films showed the greatest improvement in exudative lesions. In one instance, there was conversion despite the persistence of an open cavity.

Sensitivity tests: The sensitivity to streptomycin of all organisms was tested before, during and after the treatment period (table 2). Before treatment, the growth of tubercle bacilli was inhibited by from 0.6 mcg. streptomycin per cc. to 3 mcg. per cc. The organisms from 3 patients were inhibited only by 3 mcg., from 4 others by 2 mcg. and from the remaining 13 by less than 2 mcg.

After streptomycin had been administered for one month, tubercle bacilli from 15 patients were sensitive to less than 10 mcg. streptomycin per cc. but the inhibition level had increased from two to fourfold in each. After sixty days' treatment, the organisms from one other patient had similarly become significantly more resistant.

At the termination of the treatment period, there was an impressive increase in resistance to streptomycin in all 9 patients who were still expectorating positive sputa. In one instance the organisms grew in concentrations of 1,000 mcg. streptomycin per cc. and in 3 others in concentrations between 100 and 1,000 mcg. The remaining 5 strains were inhibited by between 20 and 100 mcg. streptomycin per cc. These observations will be further discussed later on.

In another patient there was a clinical relapse within one week after treatment stopped. Sputum again became positive, sedimentation rate increased, temperature became elevated, he began to lose weight and X-ray film showed a reactivation of the process which, during treatment, had retrogressed. Sensitivity studies re-

ported his organisms grew in concentrations of 1,000 mcg. streptomycin per cc. This suggests that development of resistance may be sudden and in some cases can be correlated with the clinical course.

One interesting observation was that the two specimens of sputa which contained markedly resistant organisms at the end of 120 days' exposure to streptomycin became less resistant during the next two months. The resistance of these strains dropped from over 1,000 to 500 and 260 mcg. per cc., respectively.

Blood concentrations of streptomycin during the therapy period: Two facts alone are of importance in this connection. The first is that, with the dosage used (0.3 g. streptomycin every four hours), the blood concentrations of the antibiotic were maintained at a level appreciably higher than the initial measurement of sensitivity of each organism for all hours of the day. The average level was 40 mcg. per cc. of serum two hours after injection and 10 mcg. per cc. four hours after injection. Maximal therapeutic efficacy thus could have been expected, at least for the period of time when the organisms continued to be streptomycin-sensitive (that is, below 10 mcg. per cc.) with these concentrations. The second observation was that, as treatment progressed, the specimens of blood serum taken two hours after an injection showed an increasingly higher level. Concentrations after two weeks of therapy averaged 20 mcg. per cc. of serum, whereas corresponding levels during the third month of therapy were from 40 to 60 mcg. per cc. Whether this was due to increased retention of streptomycin as a result of a possible irritant effect on the kidneys, or whether it was due to an alteration in the biological method of assaying the streptomycin remains to be determined.

Audiograms were taken periodically throughout the ten months of observation. *Caloric stimulation tests:* A modified Kobrak caloric test was used at weekly intervals during and after the therapy period. In all 20 patients, the test indicated a normal labyrinthine function prior to the administration of streptomycin. The test was performed on each occasion in the following fashion: While in a sitting position with the head inclined forward 15 degrees and tilted to one side, 5 cc. of ice water (7°C.) were injected against the tympanic membrane, and the time of onset of nystagmus was noted. A response within twenty seconds was considered normal. If no nystagmus was observed, the ear was the irrigated with ice water and the absence of eye movement two minutes after constant irrigation with 50 to 60 cc. ice water was considered an indication of absent vestibular function.

Viability of bacilli: It was the distinct impression of the bacteriologists that in some instances tubercle bacilli, after exposure to streptomycin, identifiable on direct smear of sputum, grew slowly and irregularly on culture. Their growth appeared to be inhibited. Smears of the colonies, however, did not show any abnormal forms or characteristics of the bacilli.

TOXEMIC MANIFESTATIONS

Local irritation at the site of injection proved to be of little import in this series. Although the patients experienced varying degrees of pain following the injection of different lot numbers of streptomycin, with none was it severe enough to neces-

sitate omitting a single dose. Local inflammation at the site of intramuscular injections occurred infrequently. Whenever it occurred, a change in the site of injection overcame the difficulty. No sterile abscesses were observed, and the use of procaine in the streptomycin solutions was not necessary.

Renal irritation: No patient developed significant urinary changes, nor variations in kidney function tests, which would indict streptomycin as a nephrotoxic agent. All patients excreted urinary casts at some time during the therapy period, but their appearance was transitory and the cylindruria was never considered an indication to discontinue treatment. The casts were usually of the hyaline type and were most commonly observed during the thirteenth to fifteenth week of therapy. In only one instance was albuminuria observed, and in this patient, despite continuation of therapy, it disappeared.

Patients who had pyuria prior to therapy frequently showed marked improvement during treatment.

Allergic manifestations: Six cases of dermatitis characterized by a maculopapular rash occurred during the first two weeks of treatment. Two other patients complained of pruritus at about the same period but no visible dermatitis appeared. Small doses of benadryl controlled the pruritus promptly in both instances. In one patient, a daily temperature elevation to 100°F. was observed during the height of his rash. It promptly fell to normal when the rash faded. Intermittent eosinophilia of from 5 to 11 per cent was noted in 18 patients. In no instance did sensitivity phenomena interrupt the therapy schedule nor was any reaction of sufficient severity to inconvenience the patient markedly or to concern the physician.

One case of contact dermatitis developed in a nurse handling streptomycin. This was manifested by a maculopapular rash on the flexor surface of both forearms. Because of this, it was recommended that all nurses who habitually handled the antibiotic in this hospital wear gloves during that manipulation.

Eighth nerve impairment: No case of hearing loss was found in any of the 20 patients either by subjective questioning or by objective measurements, including routine audiometric examinations.

Fourteen patients had tinnitus; in all it was preceded by dizziness. The tinnitus was unilateral or bilateral. It was usually characterized by a low-pitched ringing, and, occasionally, by high-pitched notes. In 11 of the 14 patients, the tinnitus, although inconstant, persisted throughout the post-therapy period of observation.

Dizziness appeared in 19 of the 20 patients. The sensation, difficult to describe, was characterized by a feeling of "full headedness" and "unsteadiness" rather than by true vertigo. The feeling of constant motion was not present and past pointing was not a part of the syndrome. Consequently, this could not be considered similar to the type of vertigo usually characteristic of vestibular dysfunction. The sensation closely paralleled other signs of that disorder, however, and was considered to be a symptom of that disorder. The onset of dizziness occurred between the eleventh to the ninety-ninth day of therapy but, in the majority, was during the third and fourth week. It has

persisted in 8 patients during after-treatment observation, but, in the remaining 11, it disappeared after persisting for from one day to one month. Following its onset, the dizziness reached a peak of severity, usually within a few days, then leveled off for about a week and, thereafter, gradually decreased. Its intensity during this period was influenced by the position of the patient in bed. Relief was obtained by lying flat, rather than by supporting the head on a pillow. Nausea or vomiting accompanied the dizziness in 3 instances, and numerous patients refused an occasional meal during the height of the syndrome.

Seventeen of the 20 patients experienced a sense of imbalance in the dark. This symptom did not make its appearance until after two months of treatment and it has persisted in 11 patients. Despite the eventual disappearance of the sensation of imbalance, most of the patients are unable, when blind-folded, to negotiate a straight line in heel-to-toe fashion. Awkwardness is quite marked. The one patient who did not complain of vertigo, dizziness or tinnitus, experienced similar difficulty in performing the above test accurately, indicating, of course, that his labyrinthine function was also damaged.

Despite this uniform subjective evidence of vestibular dysfunction, in only 9 of the 20 was objective evidence of damage obtained by caloric stimulation tests, and in only 3 of these was the loss of function complete.

Blurring of vision was a common complaint. It was often associated with a glassy stare and a decrease in mental acuity and apparently was most severe when dizziness was at its peak. It was present in 14 patients. Distant objects appeared blurred and focusing on objects at a distance of 20 feet was difficult. It persists to a mild degree in 4 patients. This phenomenon was entirely subjective, there being no accompanying objective findings in the eyes. It is difficult to picture any connection between this symptom and the vestibular nerve damage, but, as it so closely paralleled the other vestibular symptoms, it has been assumed that it was part of the syndrome. A horizontal nystagmus was observed in 3 patients at the time when blurring of vision developed. This was, however, present but for brief periods.

Miscellaneous reactions: Circumoral paresthesia was noted by 13 patients in the series during the course of streptomycin therapy. Their description of the symptom varied. A feeling of stiffness about the mouth and in the facial muscles, and a sensation of rawness in the roof of the mouth, were common accounts. In most cases it disappeared within forty-eight hours and in no case did it persist longer than two weeks. It was usually first noted early in the course of therapy but in 3 patients it appeared only 100 days after treatment was started.

Headaches were reported by 16 patients during the second month of treatment and persisted during the remainder of therapy and during the subsequent observation period. They were mild, causing the patient no appreciable discomfort. They occurred once to three times weekly and lasted for a few hours. Although usually frontal, they were generalized in 2 instances.

FOLLOW-UP OBSERVATIONS

Therapy for pulmonary tuberculosis was continued for 150 days in one patient. His roentgenograms showed satisfactory improvement, particularly of the exuda-

tive component, after 120 days' therapy but, because his cavity was still open and because regression was continuing at that time, an added month of therapy was considered to be indicated. In retrospect, it was difficult to estimate whether the extra streptomycin produced added benefit or not. His exudative disease resolved further during the fifth month but, following cessation of streptomycin, it continued to resolve at the same rate and the cavity was unaffected.

With this one exception, treatment of all patients terminated after 120 days. During the follow-up period, which averaged ninety-nine days, 15 patients continued to improve roentgenographically, and 4 others maintained the improvement gained during treatment.

The single relapse occurred one week following cessation of therapy. It was of minimal extent and occurred in a young, white male whose moderately advanced disease had shown relatively rapid progression prior to treatment with streptomycin. The exudative component of this bilateral disease had, however, resolved considerably during therapy. His sputum was positive throughout treatment and markedly resistant tubercle bacilli were found in it at the termination of treatment.

DISCUSSION

Our clinical material consisted of 20 patients with unstable pulmonary lesions. During three months of observation in our Hospital prior to streptomycin therapy, 10 had shown roentgenographic evidence of progressive disease, and 10 had failed to improve. Their disease was graded as far advanced in 15 and as moderately advanced in 5.

Definite roentgenographic improvement occurred when streptomycin therapy was instituted. The exudative lesions were most markedly affected, disappearing wholly in 4 instances (20 per cent), becoming very appreciably less in 14 (70 per cent) and showing progression in but one. The beneficial effect upon proliferative lesions and upon cavities was less definite. Sputum, previously positive for tubercle bacilli in all patients, was converted to negative in 11 (55 per cent). In the clinical changes occurring during treatment were equally favorable.

More than two-thirds of the patients, elevated temperature returned to normal, cough and sputum production were reduced and considerable increases in body weight (averaging 20 pounds) took place. The patients were impressed by the "tonic" effects of streptomycin.

In so far as one may generalize from such a small series, it is our opinion that streptomycin has been demonstrated to improve the type of pulmonary tuberculosis which was the subject of investigation. The permanence of this effect remains to be seen, but only one relapse has occurred in an after-treatment observation period averaging ninety-nine days.

Excepting only an interference with vestibular function, toxic manifestations of streptomycin therapy have, thus far, been negligible in our series. Delayed anaphylactic phenomena or renal damage may, of course, develop later. The vestibular damage is impressive and its persistence throughout the period of after-treatment observation leads us to fear that it may be permanent. It was subjectively present in 19 of the 20 cases, although, for some reason not clear to

us, it was demonstrable by the caloric stimulation test in only 9. We view it with sufficient concern so that we would be disinclined to give streptomycin to patients who may be reasonably expected to improve with other forms of therapy. The hazard of the disease must exceed the hazard of streptomycin in order to justify its use.

The development of resistance to streptomycin by the infecting bacilli is another disadvantage of this therapy. We have observed, without exception, that tubercle bacilli, isolated from patients after thirty to fifty days of treatment, have become two to four times more resistant to streptomycin *in vitro* than they were before treatment. After 120 days, this resistance has gained extremely high levels in some patients.

Unfortunately, a study of our data does not permit any definite conclusion on the important question as to whether the development of the *in vitro* resistance is accompanied by a similar resistance *in vivo*. The 2 patients whose bacilli developed an extremely high resistance to streptomycin during the therapy period, did not do well. One showed improvement for four months, but within one week of cessation of streptomycin therapy, a reactivation of his disease developed. At the end of four months' observation in the post-therapy period, X-ray films indicated his disease to be as extensive as during the pre-treatment period. In the second patient whose organisms were not inhibited by 1,000 mcg. streptomycin per cc., the large cavity present before treatment increased in size during treatment. A third patient whose organisms developed resistance to over 100 mcg. showed a similar course. These 3 patients would suggest that, when *in vitro* resistance is great, therapy with streptomycin is useless. It is also consistent with this suggestion, that these patients showed significant improvement of their disease during the first sixty days of treatment before any considerable resistance had developed. On the other hand, there was at least one patient whose disease, despite the development of resistance to over 100 mcg. per cc., did remarkably well throughout the observation period. In another instance, despite a continued sensitivity of the bacilli to below 10 mcg. for the 120-day exposure period, a new cavity developed. Finally, the patient whose exudative disease markedly resolved and whose cavity was lost to view during the treatment had bacilli which were inhibited only by 40 to 60 mcg. streptomycin per cc. after ninety days' exposure to streptomycin in the host. It can be seen from these paradoxes that our series is of little assistance in reaching a final decision on this subject.

It was not even expected that streptomycin would completely sterilize active infections or repair damaged pulmonary tissue. It acts, in our opinion, as a bacteriostatic agent which aids in temporarily controlling the infectious agent and, during this period, it may be hoped that the body will mobilize its own defense mechanisms sufficiently to handle the infection after streptomycin is withdrawn or when the bacilli become resistant to its action. With this understanding, streptomycin should prove to be a valuable therapeutic accessory to the treatment of tuberculosis.

Many problems need answers before the precise place of streptomycin can be defined. It is not within the scope of this paper to discuss ideal dosage or the

duration of treatment, nor are any leads to the answers to these questions found in this particular series. Further investigations are essential.

SUMMARY

1. Clinical, laboratory and roentgenographic observations in 20 patients with pulmonary tuberculosis who were treated with 1.8 g. streptomycin daily for four months have been reviewed.

2. Definite improvement was observed in exudative lesions in 19 patients and in 4 of these the lesions disappeared. Maximal improvement occurred after two months of therapy.

3. Improvement in proliferative disease and of cavities was neither uniform nor marked.

4. Marked clinical improvement occurred in the majority of patients within the first few weeks of therapy and continued thereafter.

5. Sputum conversion, by smear and culture, occurred in 11 patients.

6. During an average of ninety-nine days of after-treatment observation, improvement was progressive in 15 of the 20 patients and was maintained in 4. A relapse occurred in one patient.

7. Streptomycin produced vestibular damage in all patients. This has persisted following treatment and may be permanent. Its occurrence distinctly limits the usefulness of streptomycin, at least on the regimen which was employed in this series.

8. No other important toxic manifestations of streptomycin were encountered.

9. Tubercle bacilli rapidly develop *in vitro* resistance to streptomycin. The significance of this observation is discussed.

10. Streptomycin is not a specific cure for pulmonary tuberculosis. Its use was, however, accompanied by definite clinical, laboratory and roentgenographic improvement in our patients, and we believe it will have a specific place in the phthisiologist's therapeutic armamentarium.

SUMARIO

Tuberculosis Pulmonar Tratada con Estreptomicina: 20 Observaciones

1. Repásanse las observaciones clínicas, radiográficas y de laboratorio en 20 tuberculosos pulmonares tratados con 1.8 gm. diarios de estreptomicina durante cuatro meses.

2. Obsérvese mejoría bien definida en las lesiones exudativas de 19 enfermos, desapareciendo las mismas en 4 de ellos. La mejoría máxima se presentó al cabo de dos meses de terapéutica.

3. La mejoría en la forma proliferativa de la enfermedad o en las cavernas no fué ni uniforme ni pronunciada.

4. En la mayoría de los enfermos se presentó pronunciada mejoría clínica a las pocas semanas de terapéutica, continuando después.

5. En 11 enfermos se notó viraje del esputo, estudiado en frotos y cultivos.

6. Durante un promedio de 99 días de observación subsiguiente, la mejoría continuó en 15 de los 20 enfermos y se mantuvo en 4. Hubo una recidiva.
7. La estreptomycinina produjo lesión vestibular en todos los enfermos, la cual ha continuado después del tratamiento y puede ser permanente. Su aparición limita decididamente la utilidad de la droga, por lo menos con el régimen utilizado en esta serie.
8. No se encontraron otras importantes manifestaciones toxémicas debidas a la estreptomycinina.
9. Los bacilos tuberculosos desarrollan rápidamente resistencia a la estreptomycinina *in vitro*, fenómeno este cuya importancia se discute.
10. La estreptomycinina no es un remedio específico contra la tuberculosis pulmonar, pero su empleo fué seguido de bien definida mejoría clínica, radiográfica y de laboratorio en esta serie, y en opinión de los AA. tendrá su puesto específico en el arsenal terapéutico del tisiólogo.

STREPTOMYCIN IN THE TREATMENT OF PULMONARY TUBERCULOSIS^{1,2}

A Therapeutic Review of 23 Patients

CHRISTOPHER PARNALL, JR., BENJAMIN L. BROCK AND
RALPH E. MOYER

In July 1946, the Veterans Administration Hospital at Oteen, North Carolina was invited to become one of the group of Federal hospitals undertaking a cooperative study of streptomycin in the treatment of pulmonary tuberculosis. This report is a therapeutic review of the first 23 patients treated at this Hospital under the terms of this study. It was carried on concomitantly with an investigation into the effects of streptomycin upon tuberculous draining cutaneous sinuses, which has already been reported (1). There was no duplication of patients in the two series.

SELECTION OF PATIENTS

All patients selected for streptomycin therapy had been observed in this hospital for at least ninety days prior to its institution. No significant change was made in their treatment during that time. All were maintained at bed-rest during the observation period as well as through the period of treatment which followed it. Most, but not all, of the patients were moved to a separate ward immediately before streptomycin was administered, but routine nursing care and diets were not changed. In 2 patients, pneumothoraces had been induced six months previously. They were continued throughout the next six months and the same degree of collapse maintained. In these 2 patients, streptomycin was administered for treatment of lesions in the contralateral side, and no attempt was made to evaluate the effect upon the collapsed lung.

Twenty patients received streptomycin for the prescribed 120 days and 3 others for ninety days. Of the 3 with incompleated treatment, one patient left the hospital against medical advice, one was transferred and the third patient, after receiving ninety days' treatment, requested that it be discontinued. Five other 20 have been followed for from thirty days to 210 days, with an average post-therapy period of 128 days.

On the basis of pre-treatment serial roentgenograms, the pulmonary lesions were considered to be spreading in all patients at the time streptomycin treatment was instituted. Two patients had been having intermittent and more or less serious pulmonary hemorrhages previous to treatment. The series included 9 instances of far advanced disease, 12 of moderately advanced disease and 2 of

¹ From the Department of Medicine and Surgery, Veterans Administration Hospital, Oteen, North Carolina.

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minimal tuberculosis. In addition to their pulmonary lesions, 3 patients had ulcerating tracheo-bronchial tuberculosis and one of the 3 had severe, active tuberculous enteritis. There were 22 males and one female. Their ages ranged from 19 years to 53, 14 being under 30 years and 4 over 40. Twenty-one were white, 2 Negro.

Exudative disease was present, according to X-ray appearance in all cases, including the 2 with minimal lesions, but there was no case with a massive pneumonic lesion. Single or multiple cavitations were present in all patients with far advanced tuberculosis. In 3 patients with moderately advanced disease, there were single cavities. In 4 individuals, during the three months' pre-treatment observation period, sizable areas of new disease had developed in previously uninvolved lung. Associated proliferative, caseous and fibrotic disease was present in most cases.

All patients reacted to tuberculin before and after treatment.

The criteria for selection of patients and the preliminary laboratory procedures called for by the protocols, as described in the introductory paper of this series, were complied with. Throughout the therapy period and during its follow-up, as many of the suggested procedures were performed as were feasible. Sensitivity tests of the bacilli were, however, not performed.

RESULTS

1. Three patients received only ninety days' therapy, 2 because they left the hospital at the end of that time and, the third, because he refused to accept more.

The first patient, the youngest in the series, had increasing, moderately advanced pulmonary tuberculosis with a small, recent and thin-walled cavity (figures 1A and B). During the period in which he received streptomycin, his X-ray films revealed progressive clearing of the exudative lesions and closure of his cavity (figure 1C). His sputum became negative by smear and culture after three weeks' treatment. Serial bronchoscopies demonstrated that his tracheo-bronchial lesion cleared completely within six weeks. This was regarded as an excellent immediate result in a young person in whom previous conservative therapy had failed to control progressive disease.

The second patient who received ninety days' therapy had moderately advanced unilateral disease without cavitation. It was estimated that about 50 per cent of his total disease resolved during therapy and that only proliferative and fibrotic lesions remained. His sputum was converted to negative on smear and by culture at the time of his discharge. He had improved to a lesser extent than the first, but in both patients the course of the disease was favorably reversed. It has been impossible to make follow-up observations in either one.

The third patient refused further treatment after ninety-one days' therapy. Throughout the course of therapy for a far advanced and progressing bilateral tuberculosis, the patient had, intermittently, blood-streaked sputum, a complication which had also been observed prior to therapy. Despite these hemoptyses, his total disease cleared remarkably while he was receiving streptomycin and his sputum became negative by concentration and



FIG. 1. Case 1. White male, aged 19.

- A. (Upper left) Roentgenogram of June 21, 1946, showing exudative tuberculosis, right upper lobe.
- B. (Upper right) Roentgenogram of July 10, 1946, showing excavation within same area. One and eight-tenths g. streptomycin administered daily from July 21, 1946 to October 21, 1946.
- C. (Bottom) Roentgenogram of October 14, 1946, made just prior to cessation of treatment. Note closure of cavity, marked resolution of exudative disease, and residual small areas of infiltration.

culture. Five months following cessation of therapy, a massive pulmonary hemorrhage resulted in rapid exsanguination and death. In that interval, the patient had maintained the improvement shown by X-ray films during treatment, but his sputum became positive two months after its termination. Autopsy revealed the site of bleeding to be a large, eroded vein at the lower pole of a small residual cavity in the left upper lobe of the lung. Streptomycin could not be indicted as a cause of this death.

All of the other 20 patients were treated for 120 days and observed for an average of 128 days subsequent thereto. The remainder of this report will concern itself with the observations made upon them.

2. *Clinical observations:* Seventeen of the 20 patients had daily elevations of temperature to 101° or 102° F. during the pre-treatment observation period.

TABLE 1
Clinical results

FINDING	INCIDENCE	
	Number	Per cent
Temperature:		
Normal throughout.....	3	15
Reduction.....	17	85
Reduction to normal.....	15	75
Cough and sputum:		
Decrease.....	18	90
No change.....	2	10
Sedimentation rate:		
Normal throughout.....	0	0
Rate slowed.....	14	70
Rate returned to normal.....	6	30
No change or elevated.....	6	30
Sputum conversion:		
Negative by smear and culture.....	12	60
Negative smear, positive culture.....	2	10

Within two weeks of commencing streptomycin therapy, the temperature was reduced in all 17 patients and in 15 instances it returned to normal (table 1).

Marked reduction in cough and sputum occurred in 18 patients and was similarly prompt in its appearance (table 1). In 3 instances cough had been distressing and painful and sputum production had amounted to from 50 to over 100 cc. daily. These symptoms were reduced to negligible complaints within six to eight weeks, and in 3 of the patients it was necessary to resort to gastric lavage after the third month in order to examine pulmonary secretions.

Appetite improved in all 20 patients and all remarked upon a returned sense of well-being. Nine patients gained weight, the greatest increase being 41

pounds and the average of the 9, 11.8 pounds. Eight other patients maintained satisfactory weight but did not gain. In 3 patients, who did the least well as far as radiological results were concerned, weight loss up to 10 pounds occurred. It should be emphasized that these improvements occurred in a series of patients whose clinical condition was deteriorating at the time streptomycin was added to their treatment.

3. *Laboratory observations:* (a) Sputum conversion (table 1): Tubercle bacilli were demonstrated in the sputum of all patients during the pre-treatment observation period by direct smear and subsequently confirmed by culture. At the end of the 120-day treatment period, 12 of the 20 patients had negative specimens, and in 2 others, tubercle bacilli could be found only by culture. In the remaining 6 instances, there was a marked reduction in the number of bacilli found on single examinations.

This observation was impressive. The sputa of 12 patients whose lesions were predominantly exudative, including the 2 with minimal lesions, were converted to negative. The sputa of 8 patients with cavities were not converted even though 3 of them had extensive exudative components which, as will be described later, resolved exceptionally well.

(b) Sedimentation rates: Sedimentation rates were abnormally high in all patients before the therapy period; 14 rates were significantly decreased and 6 of them returned to a normal range during streptomycin therapy.

(c) Eosinophilia: Eleven patients were observed to have eosinophil counts above 6 per cent for varying periods during the course of streptomycin therapy. The percentage varied in each patient, occasionally reaching levels as high as 25 per cent. It appeared any time after the first week of therapy and persisted for periods ranging from a few days to several weeks. In some patients it persisted throughout the treatment period; in others, it was only intermittently observed.

(d) Varying numbers of casts appeared in the urine specimens of all patients at some time during the treatment period. They appeared within the first week in most instances, but in others they were excreted only after a month or six weeks of therapy. For the most part, once they were noted, they persisted until streptomycin was discontinued. In a few instances they appeared intermittently, being present for from a week to ten days, then disappearing for similar periods, only to recur. The hyaline type of cast was the one most frequently encountered. Albuminuria was not observed in any patient. It was soon found that the number of casts excreted varied as the pH of the urine was altered. In acid urine, casts were more numerous and more persistent. When, with the use of alkalinizing agents, the urine was maintained at a pH above 7, the number of casts decreased; this decrease took place within a few hours following the first production of the alkaline urine. So reproducible were these observations that there can be no doubt about their correctness. A serious attempt was therefore made to keep the urine alkaline throughout the 120-day treatment period with the design of preventing more serious kidney damage (2). It is probable, however, that we did little more than demonstrate

the solubility of hyaline casts in an alkaline medium, for tubule fluid does not become alkaline until it has reached the distal segments, and casts are supposedly formed in regions proximal to that point.

(e) Routine measurements of the concentration of streptomycin in the blood serum were performed throughout the treatment period in all patients. The average concentration one hour after injection was 15 mcg. per cc. of serum; four hours after injection, it averaged 5 mcg. per cc.

(f) Other laboratory procedures, including complete blood counts, blood urea-nitrogen determinations, urea clearance tests, bromsulphalein liver function test, and audiometric examinations were done at regular intervals throughout the period of study. In no instance was an abnormal finding of any of these

TABLE 2
Roentgenographic results

TYPE OF DISEASE	NUMBER	PER CENT
Cavities.....	11	100
Closed or lost to view.....	3	27.3
Smaller.....	2	18.2
Unchanged.....	4	36.3
Larger.....	2	18.2
Exudative lesions.....	20	100
Complete resolution.....	3	15
Marked regression.....	12	60
Minimal or no change.....	4	20
Extension.....	1	5
Proliferative lesions.....	5	100
Smaller.....	1	20
Unchanged.....	4	80
Larger.....	0	0
New lesions.....	1	100
Pleural effusion.....	1	100

recorded, indicating that streptomycin had produced no damage to bone marrow, kidney function, liver or hearing.

4. *Roentgenographic observations:* (Table 2.) The serial X-ray films taken during the ten months of the study were reviewed by two groups of physicians. The hospital staff recorded their findings each month, and a group of physicians from Asheville and Black Mountain, North Carolina was asked to judge the results of therapy after its completion. The group was well acquainted with both the clinical and roentgenographic aspects of tuberculosis and, as they were not directly concerned with the study, their critical evaluation of the results are considered especially valuable. The opinions of Drs. Julian A. Moore, Paul H. Ringer and N. L. Anderson of Asheville and Dr. Charles D. Thomas

TOXICITY

Nineteen of the 20 patients in the series demonstrated one or more toxic manifestations resulting from the long-term administration of streptomycin (table 3). None was severe enough to require the cessation of treatment, but each aroused a considerable degree of concern in both the patient and the physician.

(a) *Eighth cranial nerve involvement:* Vestibular function was diminished or abolished in 19 of the 20 patients, and this dysfunction persisted in 13 after the end of treatment.

TABLE 3
Toxic manifestations in 28 patients receiving streptomycin for from 90 to 120 days

MANIFESTATION	INCIDENCE	
	Number	Per cent
Phenomena of sensitivity:		
Eosinophilia.....	7	30
Maculo-papular rash with eosinophilia.....	4	18
Other.....	0	
None.....	12	52
Renal:		
Casts.....	23	
Albuminuria.....	0	100
Decreased function.....	0	
Vestibular impairment:		
Caloric stimulation test—		
absent response.....	8	35
diminished response.....	13	56
Tinnitus.....	14	61
Dizziness, blurred vision and ataxia.....	21	91
None.....	2	9

During the pre- and post-therapy period, as well as at weekly intervals during the treatment, a modification of the Barany caloric stimulation procedure was performed. This method included the injection of small amounts of lukewarm water (65° F.) against the ear drum. The onset of a lateral nystagmus was measured in seconds, twenty to thirty being considered normal.

In 7 patients, an absent response to caloric stimulation was noted at the end of four months' treatment and, in at least 4 of these, it was noted after one month. In 12 other patients, there was a delayed reaction to the stimulus but complete absence of nystagmus was not observed. In the remaining patient, the response was normal at all times.

In 19 patients, a syndrome characterized by the simultaneous onset of three distinct symptoms—dizziness, ataxia and blurred vision—occurred. Each symptom was variously described by different individuals but had certain com-

mon denominators. Dizziness was reported to be a feeling of unsteadiness, with a sensation or fear of being unable to stop a directed motion at the desired point. On turning over in bed, for example, the patient felt as though he could not prevent a complete rotation, although, in fact, he could do so. It was similar to, but not identical with, true subjective vertigo. Sudden changes in position exaggerated the sensation. Ataxia was also a subjective observation. The patients believed that they walked with an irregular and unsteady gait and had the sensation of drunkenness. In fact, they were unable to walk a straight line, but the ataxia was worse subjectively than could be measured objectively. Blurring of vision could not be measured. Again the patient stated that he was unable to focus on distant objects but no ocular abnormality could be found on examination. This part of the syndrome was worse when the patient was walking.

Tinnitus was an associated symptom in 14 patients, but it was irregular in its onset and duration. It was never disabling, only bothersome, and usually lasted but a short time. Nausea and vomiting were not encountered and hearing loss was not noted.

The diagnosis of disturbed labyrinthine function could not always be made early in the course of its existence by the results of caloric stimulation tests. Five patients, 2 of whom had very severe symptoms, did not develop abnormal responses until after the cessation of therapy. It may have been that the test utilized was an ineffective one or that it was not performed correctly but, in our hands, the subjective evidence of disturbed labyrinthine function was more important than any functional tests that were performed. In contrast to the frequently delayed abnormal response to the caloric tests, the onset of the triad of dizziness, ataxia and blurred vision developed within the first four weeks of treatment in 12 patients. The others first noted the symptom before the end of the second month of treatment.

The majority of patients noted a gradual reduction in the symptoms of the eighth nerve damage within a month after their onset, but in 13 patients they were present in varying degrees at the end of therapy. Their awareness of the disability was aroused only when rehabilitation was started, although, frequently, sudden changes in position or motion brought back a fleeting sensation of vertigo. Following the cessation of therapy and for the entire 120 days thereafter, the labyrinthine function, as measured by the caloric stimulation test, was completely abolished in 7 patients and markedly reduced in 5 others. All these patients had true nocturnal ataxia and diurnal visual disturbances when in motion.

Of the 20 patients, 7 compensated for the disability very well. These patients have no symptoms and have become able to perform all essential activities. None, however, has as yet returned to society and it is difficult at this time to predict how effective an economic life they will be able to lead. Three patients continued to have dizziness and are seriously incapacitated seven months after completing treatment. It is significant that the patients most seriously affected by this complication were either in the older age group or were the lightest in weight.

(b) *Allergy*: Four patients developed diffuse maculo-papular rashes over the torso on the fourth, seventh, eighth and thirtieth days of therapy. Treatment was continued in these patients. The rashes disappeared without specific treatment within four or five days and did not recur. Eosinophilia without a rash appeared in 7 other patients. Its range varied from 6 to 25 per cent. None of these patients manifested any other type of allergic reaction. Fever, which could be attributed to streptomycin sensitivity, was not observed.

No other types of delayed anaphylactic phenomena were observed (2) and no allergic reaction of any type caused an interruption of therapy. No other toxic reactions were observed in this study.

FOLLOW-UP OBSERVATIONS

At the end of the treatment period, it was the consensus that 7 patients had quiescent tuberculosis, having experienced marked resolution of exudative lesions and a reduction in the extent of the remaining lesions as well as having negative sputa. Twelve other patients had shown a minimal to marked degree of improvement but, on radiological grounds, they were believed still to have active tuberculosis despite negative sputa in 10 (one of these died). Three patients had not shown any X-ray improvement although each had appreciable symptomatic improvement and the progressive course of their disease was halted. The remaining patient, although the progression of his disease may have been slowed, was relatively refractory to treatment. In addition to these observations, in 3 patients tuberculous tracheo-bronchitis had apparently healed and in one patient the symptoms of enteritis were entirely relieved.

Twenty of the 23 patients were observed for 128 days following the completion of treatment. Reactivation and definite spreads or extensions occurred in 4 instances. Three of these were of minimal degree but the fourth was more severe.

It took place in a patient (figure 2, case II) whose moderately advanced disease prior to therapy had shown rapid progression to a far advanced stage, and who had a recent spread to the opposite lung, in which a small cavity appeared immediately before streptomycin was administered (figure 2A). During the treatment period, there had been moderate resolution of the exudative disease (figures 2B and C) and cavity shrinkage, but the total picture was somewhat disappointing in the sense that we had expected disease of this type to respond particularly well. His sputum had not been totally converted although the direct smears were negative at the time treatment was terminated. Within a week following the last injection of streptomycin, X-ray films showed a definite increase in extent of disease and the cavity increased markedly. Sputum smears again became positive and he developed other evidences of reactivated tuberculosis. One month after stopping streptomycin, during which time the lesions slowly progressed (figure 2C), pneumoperitoneum was instituted and this procedure apparently was sufficient to control the disease, for there was a gradual improvement thereafter. At the end of the 120-day period of observation, his sputum was again negative on smear and one specimen has been negative on culture.

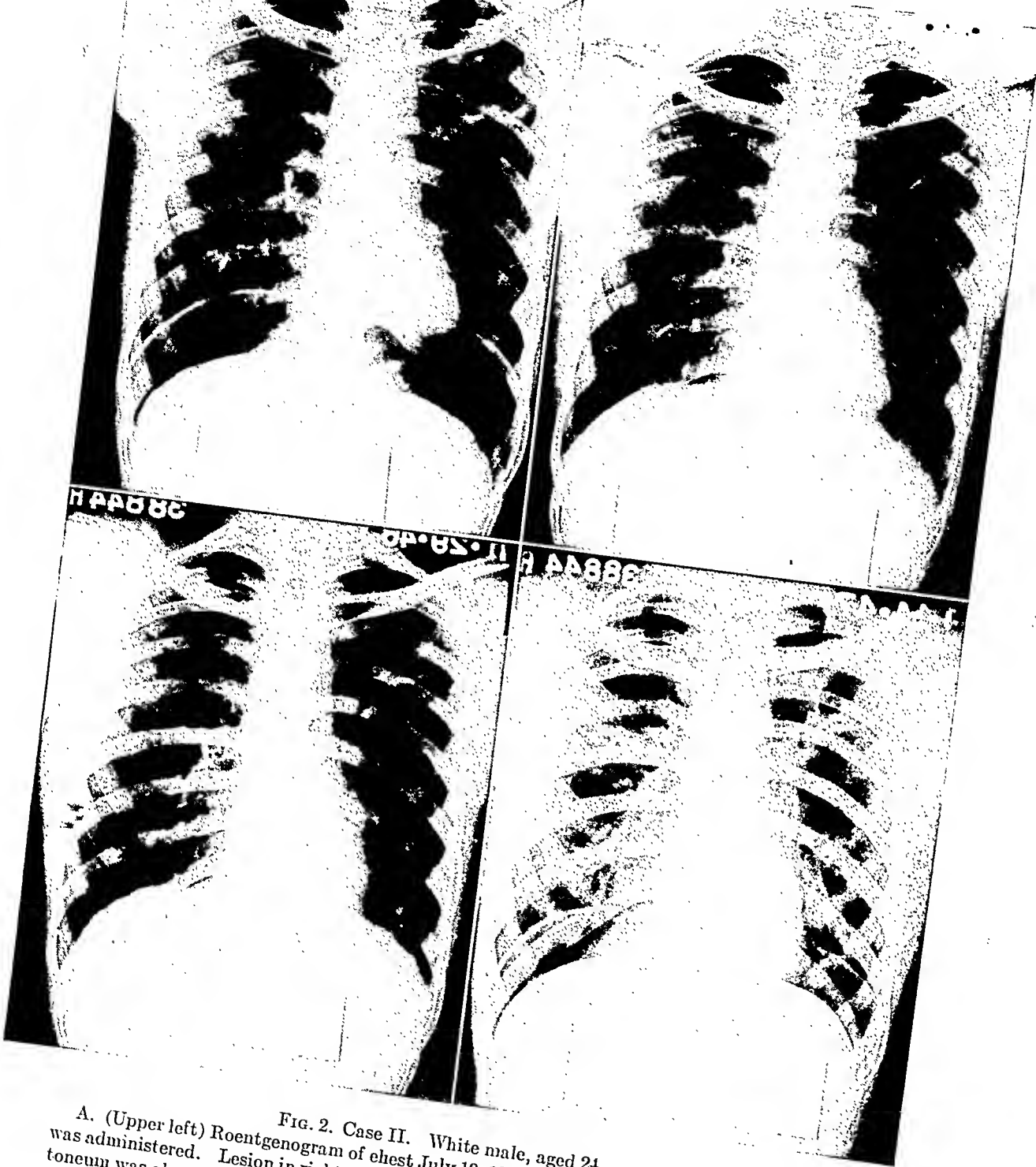


FIG. 2. Case II. White male, aged 24.

- A. (Upper left) Roentgenogram of chest July 19, 1946, taken shortly before streptomycin was administered. Lesion in right lung is of less than one month's duration. Pneumoperitoneum was abandoned after this X-ray film.
- B. (Upper right) Roentgenogram, October 18, 1946, after seventy days' treatment with streptomycin. There has been minimal regression of lesion in right lung and a marked reduction in size of cavity.
- C. (Lower left) Roentgenogram of November 29, 1946, taken after one hundred and ten days' treatment with streptomycin. Cavity is larger but there has been further resolution and organization of the exudative lesion on the right.
- D. (Lower right) Roentgenogram of January 14, 1947, taken one month after cessation of therapy, showing marked enlargement of cavity and reactivation of the lesion on the right. Pneumoperitoneum was reinstituted a few days before this film.

Two patients, aged 40 and 53, had advanced, slowly progressive disease prior to streptomycin, which with specific therapy had, in one case, become more stable and shown some retrogression. The other was the patient whom streptomycin had not appreciably benefited. At the end of the treatment period, sputa were positive in both, a cavity was open in one, and had become slightly larger in the other. Within thirty days following cessation of therapy, there were definite small spreads and reactivations in both patients. During the second month following treatment, pneumoperitoneum was established in each and a phreniclasia in one. These procedures have aided in stopping the progression, but no improvement has been noted in either.

The fourth relapse occurred in the only female in the group. She had minimal progressive disease prior to streptomycin, which, with treatment, had shown regression. Her sputum had been converted. One month following the completion of therapy, her sputum became consistently positive again, although there has as yet been no clinical or roentgenographic evidence of extension of the disease.

All of the remaining patients in the series have maintained the improvement noted during the treatment period and, in 12, the disease has continued to improve. It will, however, be necessary to induce some form of collapse measure in 5 patients to obtain permanent control of the disease. It is estimated that one of these could not have had it without the therapeutic help of streptomycin.

DISCUSSION

In discussing the results of treatment in our series, it must be emphasized that 19 of 20 patients demonstrated some type of improvement, according to clinical, laboratory or roentgenographic findings, during the period of streptomycin treatment. Although it is recognized that tuberculosis is a variable and unpredictable disease in the human, and that isolated cases of improvement are not unusual, it was the consensus of all who followed these cases that they had never before seen any treatment measure induce such consistent improvement. Yet all of these patients were selected for therapy at a time when their disease had been observed for a sufficiently long period of time at bed-rest to determine that the course of the disease was certainly not improving. These results are consistent with Hinshaw's hypothesis (1) that, by exerting a "suppressive" effect on the tubercle bacillus, streptomycin alters the progress of the disease in man.

On the other hand, we have been so impressed by the residual damage imposed by streptomycin upon the balancing mechanism, which, in our experience, would appear to be a permanent effect, that our insistence upon a proper selection of cases must be emphasized. It is our feeling that the greatest usefulness of streptomycin will be in the management of those patients who do poorly with accepted minor collapse procedures but who are too ill for major surgical procedures and that a combination of drug therapy with surgery should be investigated.

The optimum dosage of streptomycin is not yet known. A reduction in both the total daily dose and the duration of treatment should be investigated in the

hope that toxicity may thereby be diminished or avoided. The 3 patients in this series who received ninety days' therapy apparently benefited as much as those who received longer treatment.

SUMMARY

1. Twenty-three patients with progressive or stationary pulmonary tuberculosis have been treated with 1.8 g. streptomycin daily for from ninety (3) to 120 (20) days and have been followed for an average period of 128 days thereafter.
2. There was one death in the series, due to exsanguination following pulmonary hemorrhage. The death could not properly be attributed to streptomycin since it occurred five months after completion of treatment.
3. Streptomycin in the treatment of pulmonary tuberculosis has proved to be of great benefit in many instances, less so in others, but only one patient did not improve in some fashion. Fifty-five per cent converted their sputum from positive to negative, by smear and culture; temperature was reduced to normal in 88 per cent of those who had fever; cough and sputum production decreased in 90 per cent; and 45 per cent gained an average of almost 12 pounds in weight during the treatment period. Three of the 11 cavities (27 per cent) closed and 2 (18 per cent) became smaller. Exudative lesions resolved completely in 3 instances (15 per cent) and were markedly smaller in 12 others (60 per cent).
4. In the follow-up period, 2 patients were lost and their respective courses could not be observed; 4 patients had extension of their disease; one died; and 16 patients either maintained the improvement gained during the period of treatment with streptomycin or continued to improve.
5. The onset of prolonged vestibular dysfunction as a result of streptomycin therapy has been described and its importance discussed. Because of this effect, a careful and proper selection of cases for therapy is necessary to utilize streptomycin intelligently in the treatment of tuberculosis.
6. Streptomycin is the first drug which has been proved to alter the course of human pulmonary tuberculosis.

SUMARIO

La Estreptomicina en el Tratamiento de la Tuberculosis Pulmonar: 23 Observaciones

1. Veintitrés enfermos con tuberculosis pulmonar evolutiva o estacionada fueron tratados con 1.8 gm. diarios de estreptomicina por espacio de 90 (3) a 120 (20) días, siendo observados por un período subsiguiente que promedió 128 días.
2. Hubo una muerte en la serie, debida a desangramiento consecutivo a una hemorragia pulmonar. La muerte no puede imputarse justamente a la estreptomicina, pues sobrevino cinco meses después de terminar el tratamiento.
3. En el tratamiento de la tuberculosis pulmonar, la estreptomicina resultó de mucho beneficio en muchos casos y de menos en otros, pero un solo enfermo no mejoró en alguna forma. En 55 por ciento viró el esputo de positivo a nega-

tivo, en frotos y cultivos; la temperatura bajó a normal en 88 por ciento de los casos febriles; la tos y el esputo disminuyeron en 90 por ciento; y 45 por ciento aumentaron en peso un promedio de casi 5.5 kg. durante el período de tratamiento. Tres (27 por ciento) de las 11 cavernas se cerraron por completo y 2 (18 por ciento) se volvieron más pequeñas. Las lesiones exudativas se resolvieron completamente en 3 casos (15 por ciento) y disminuyeron notablemente en otros 12 (60 por ciento).

4. En el período de observación subsiguiente se perdió de vista a 2 enfermos y no pudo comprobarse la evolución posterior; en 4 enfermos hubo difusión de la enfermedad; uno falleció, y los otros 16 o bien mantuvieron la mejoría obtenida durante el período de tratamiento o continuaron mejorando.

5. Describese la iniciación de prolongada disfunción vestibular a consecuencia de la estreptomycinoterapia, discutiéndose su importancia. Debido a la misma resulta necesaria una selección cuidadosa de los casos que van a recibir estreptomicina, a fin de utilizar esta terapéutica inteligentemente en la tuberculosis.

6. La estreptomicina es la primera droga que se haya demostrado que altera la evolución de la tuberculosis pulmonar en el hombre.

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TREATMENT OF PULMONARY TUBERCULOSIS WITH STREPTOMYCIN^{1,2}

STANTON T. ALLISON AND J. M. N. NILSSON

Renewed interest in the chemotherapeutic attack upon disease processes arose in the mid-thirties with the discovery of sulfanilamide and, later, of other members of the sulfonamide series. The dramatic effect of these drugs upon the course of pneumococcic pneumonia and hemolytic streptococcic infections in particular, gave rise to the possibility that they might be of value in the treatment of tuberculosis. One of us (1) reported on a small series of cases of pulmonary tuberculosis treated with sulfapyridine. The results of this study were entirely negative.

As synthetic drugs of the sulfone series were subsequently produced, hopes rose and fell as they were successively tried and found wanting in effecting the arrest of tuberculosis.

Very soon after the discovery of streptomycin, and the demonstration of its bacteriostatic action against cultures of tubercle bacilli, Feldman and Hinshaw (2) reported experiments indicating its effectiveness against tuberculosis in guinea pigs and, shortly thereafter, Hinshaw, Feldman and Pfuetze (3) described its apparent usefulness in human tuberculosis. The drug gave promise of being the first genuinely effective chemotherapeutic weapon against this disease. A more extended clinical trial was urgently indicated. In the course of a coöperative attack on the problem by three Federal agencies, the Veterans Administration Hospital at Rutland Heights, Massachusetts was selected as one of the initial group of seven Study Units.

REGIMEN

The uniform protocol, designed for this study by the Federal agencies, is contained in the introductory paper of this series. We have followed its terms in the selection of cases, in the regimen employed and in the laboratory procedures performed. Our cases were, therefore, all patients under 45 years of age with bacteriologically proved disease, predominantly exudative in type, which had been observed for more than sixty days and found to be either progressive or stationary. They received 1.8 g. daily for 120 days in divided doses of 0.3 g. every four hours.

Technique of injection: The buttock and the deltoids were used as sites of intramuscular injection. During the early part of the study, a few drops of 1 per cent procaine solution were drawn up into the syringe containing streptomycin³ in order to lessen the pain of injection, but this was soon discontinued.

¹ From the Department of Medicine and Surgery, Veterans Administration Hospital, Rutland Heights, Massachusetts.

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³ Streptomycin hydrochloride "Merck" was used in this study.

as unnecessary. Most of the patients complained of some burning and pain at the site of injection during their first few weeks of therapy, but no one refused injections because of this discomfort. It usually lasted only a few moments or minutes following injection, but occasionally soreness and discomfort persisted for hours. The sites of injection were changed for each patient at each injection. No skin or deep tissue abscess developed in any of the patients, and there were no immediate reactions to the drug.

TABLE 1
Clinical material and clinical observations

PATIENT NUMBER	AGE IN YEARS	SEX AND RACE	ESTIMATED DATE ONSET TUBERCULOSIS	DISEASE N.T.A. CLASSIFICATION	SPUTUM ¹							SEDIMENTATION RATE (MM. PER HR.)					WEIGHT (POUNDS)					
					After days of treatment							After days of treatment					After days of treatment					Percent
					0 Sm. and Cult.	30 Sm.	60 Sm.	90 Sm.	120 Sm.	120 Cult.		0	30	60	90	120	0	30	60	90	120	
1	45	M/W	4/1946	F.A.	+	+	+	+	+	-	21	18	15	18	14	122	126	128	134	135	143	
2	28	M/W	4/1946	F.A.	+	+	+	+	+	-	21	10	6	10	11	100	101	101	104	105	122	
3	26	M/W	5/1945	F.A.	+	+	+	+	+	-	28	26	20	25	21	101	107	112	112	118	125	
4	43	M/W	4/1945	F.A.	+	+	+	+	+	+	23	20	21	21	22	116	120	124	126	126	126	
5	28	M/W	3/1942	F.A.	+	+	+	+	+	-	21	21	22	20	21	148	153	158	160	160	166	
6	35	M/W	1/1946	F.A.	+	+	+	+	+	-	29	28	24	17	16	106	107	117	121	125	134	
7	22	M/W	2/1946	F.A.	+	+	+	+	+	-	27	29	24	17	14	116	119	117	117	131	168	
8	29	M/W	12/1944	F.A.	+	+	+	+	+	+	20	27	25	25	23	153	149	159	171	182	183	
9	22	M/W	10/1943	F.A.	+	+	+	+	+	-	26	23	22	21	22	150	150	150	151	146	143	
10	25	M/W	8/1941	M.A.	+	-	+	-	-	-	15	16	13	5	5	133	139	142	143	142	144	
11	28	M/W	10/1946	F.A.	+	+	+	+	+	+	14	15	16	21	20	157	166	174	182	182	186	
12	20	M/W	4/1946	F.A.	+	+	+	+	+	+	18	22	21	17	19	143	144	145	148	150	147	
13	29	M/W	4/1946	F.A.	+	+	+	+	+	-	15	19	10	5	9	123	124	128	132	135	143	
14	31	M/W	3/1946	F.A.	+	+	+	+	+	-	23	23	19	18	17	100	103	108	113	123	133	
15	28	M/W	1940	F.A.	+	+	+	+	+	-	20	21	28	22	16	110	112	116	116	121	140	
16	21	M/W	8/1945	F.A.	+	-	-	+	+	-	20	23	29	23	27	117	115	112	111	111	107	
17	27	M/W	7/1946	F.A.	+	+	+	+	+	-	21	19	13	14	13	126	128	130	133	138	152	
18	32	M/W	8/1946	F.A.	+	+	+	+	-	+	12	20	23	23	20	138	147	151	157	167	178	
19	29	M/W	9/1946	F.A.	+	+	+	-	-	-	21	22	20	18	17	135	140	138	138	142	139	
20	21	M/W	3/1945	F.A.	+	+	-	+	-	-	22	21	9	8	8	109	113	118	120	118	121	

¹ Sm. = Smear.

Cult. = Culture.

+

- = Negative.

CLINICAL MATERIAL

Twenty-one patients, all white, male veterans of World War II, were selected for the study (table 1). Their ages varied from 21 to 45 years and averaged 28.5 years. The estimated duration of their disease at the initiation of streptomycin therapy was from two to seventy-two months and averaged 16.5 months.

In terms of the National Tuberculosis Association terminology, 20 patients had far advanced and one had moderately advanced pulmonary tuberculosis. They had all been observed in the Rutland Hospital for at least sixty days and, with a single exception, their disease had shown roentgenographic evidence of progression during this period of observation. In all instances, positive cultures were obtained from verified sputa or gastric lavage within thirty days prior to the start of streptomycin therapy. Thirteen patients had previously received some form of collapse therapy without favorable effect upon the course of their disease. Several patients who were selected for treatment were so seriously ill that a point had to be stretched to fulfill that criterion of the protocol which required that "each patient have a life expectancy of at least 12 months without streptomycin therapy." Treatment was started between September 26 and December 14, 1946, and, with the exception of a single patient (omitted from table 1) in whom it was stopped after thirty-two days because of a severe exfoliative dermatitis, was continued for 120 days. All but 4 of the patients have had an after-treatment observation period exceeding 120 days.

CLINICAL OBSERVATIONS

Symptomatic improvement was observed within the first two to four weeks after starting streptomycin therapy in 19 of the 20 patients who completed their 120 days of treatment. In 17 instances (85 per cent) it was marked and definite. In 2 cases it was but slight (§9 and §10, table 1) and in one (§16) no improvement occurred. All of the 17 patients reported an increased sense of well-being and had a notable improvement in appetite. In 10 cases (50 per cent), previously existing cough had disappeared at the end of one month and in the remaining 7 it was decreased in frequency and severity. The sputum was reduced in amount in 16 cases within two weeks and became negligible at the end of one month. Thirteen of the 20 patients had been running average maximum daily temperatures of above 99° F. Within two weeks of commencing therapy, 8 of the 13 became normal, in 2 fever was reduced for brief periods only to rise again and in 3 it remained unchanged. In 9 of these 13 patients, in whom the average daily temperature had been between 100° and 104° F., temperature became normal in 6 within two weeks, in 2 it was temporarily lowered and in one it remained unchanged.

In contrast to these very prompt effects upon appetite, cough, sputum and fever, the increases in body weight were slower in making their appearance. This timing is contrary to the experience of others (4) but was very definite in our experience (table 1). At the end of each of the four months of therapy, the average increase in weight of the entire group was 2.7, 6.0, 9.3 and 12.7 pounds, respectively. Eighteen patients participated in this gain and only 2 showed a loss of weight. In the 120 days of after-treatment observation, 15 patients continued to gain weight and the average gain for the entire group was 19.6 pounds.

Erythrocyte sedimentation rates (Cutler) were elevated at the commencement of therapy in all patients (table 1); the average at this time was 22 mm. in one

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hour, the lowest 12 and the highest 29 mm. At the conclusion of 120 days of therapy, the average rate was 17 mm.; 15 patients showed some reduction but in only 8 of these (40 per cent) was it considerable, and in only 3 did it return to normal range.

Specimens of sputa from all 20 patients had been positive for tubercle bacilli both by smear and culture prior to therapy (table 1). The results at the conclusion of therapy are difficult to evaluate. In only 4 patients (20 per cent) was it impossible to find bacilli in seventy-two-hour sputum concentrates. On the other hand, the cultures from these concentrates were negative in 15 cases (75 per cent). This may be interpreted to mean that a majority of the bacilli remaining at the end of therapy were non-viable or, at least, incapable of reproducing and growth. Since it is not, at the moment, known whether the strains which were positive on smear and negative on culture are capable of reproducing tuberculosis in guinea pigs or man, it is impossible to say whether a true conversion was produced in 20 or in 75 per cent of this series.

Tuberculin tests were positive in all patients both at the beginning and end of therapy, with no detectable difference in the extent of the reaction. The average streptomycin concentration of blood serum, collected two hours after intramuscular injection of the drug, was 16.24 meg. per cc., with variations from 10 to 21 meg. per cc.

ROENTGENOGRAPHIC OBSERVATIONS

The roentgenographic changes which occurred during therapy were much less dramatic than the clinical observations which have just been described. Nevertheless, definite clearing occurred in lesions which had been progressive prior to streptomycin treatment. The sequence of these changes is summarized in table 2 where it may be seen that they are progressively more favorable up to the ninety-day films. After thirty days, 3 cases were estimated as showing minimal and 3 moderate clearing. After sixty days, 10 cases were classified as improved, 7 minimally and 3 moderately. After ninety days, 15 cases showed improved, 3 minimal and 12 moderate; while 5 cases remained unchanged. Thus far there had been no new lesions or progression of disease. At 120 days, 2 cases showed some slight spread of tuberculous infection in comparison with the ninety-day films, although their disease was still less extensive than it had been initially. Of the remaining cases, 14 were graded as moderately improved and 4 as unchanged. In summary, therefore, 16 cases (80 per cent) showed improvement during the 120 days of therapy, although 2 failed to maintain their improvement.

In the 120 days of after-treatment observation, 3 patients have suffered an extension of their disease, 9 have shown no further roentgenographic change and 8 have shown continued improvement. Although all positive cultures have been frozen for subsequent determinations of their sensitivity to streptomycin, it has not yet been possible, except in one instance, to make these determinations and only in this case can evidence be adduced concerning their resistance in those patients whose disease extended during the final month of treatment or subsequent thereto.

TABLE 2
Roentgenographic observations

PATIENT	AT 30 DAYS	AT 60 DAYS	AT 90 DAYS	AT 120 DAYS	RELAPSES DURING POST-TREATMENT PERIOD
1	N.C.	N.C.	N.C.	N.C.	
2	Exud: min. clearing	Prol: smaller	Prol: smaller	Exud: def. clearing Prol: harder	
3	N.C.	N.C.	Exud: clearing Prol: harder	Exud: def. clearing Prol: harder	60 days; spread to left lung
4	N.C.	N.C.	N.C.	N.C.	
5	N.C.	Cav: slightly smaller	Cav: smaller	Cav: lost to view	
6	Exud: min. clearing	Prol: harder	L: residual fibrosis RUL: contracting	L: almost clear RUL: contracted	
7	N.C.	Exud: smaller	Cav: closed Prol: harder	Exud: smaller Prol: harder	
8	Exud: def. clearing	N.C.	Exud: clearing	Exud: def. clearing	21 days; spread to left lung
9	N.C.	Cav: smaller	Cav: smaller	Cav: lost to view	
10	N.C.	Exud: clearing	Exud: clearing	Exud: def. clearing residual fibrosis	30 days; spread to LUL
11	Cav: smaller	N.C.	N.C.	Cav: larger	
12	N.C.	Exud: slight clearing	Exud: slight clearing	Cav: larger	
13	N.C.	N.C.	Exud: marked clearing	Exud: residual fibrosis only	
14	Exud: min. clearing Prol: harder	Cav: smaller Prol: harder	Exud: smaller Prol: harder	Cav: smaller Prol: harder	
15	N.C.	N.C.	N.C.	N.C.	

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TABLE 2—Continued

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TABLE 2—Continued					
PATIENT	AT 30 DAYS	AT 60 DAYS	AT 90 DAYS	AT 120 DAYS	RELAPSES DURING POST-TREATMENT PERIOD
16	N.C.				
17	Cav: smaller Exud: clearing	Cav: smaller	N.C.		
18	N.C.	N.C.	Cav: lost to view	N.C.	
19	N.C.		Exud: clearing	Exud: residual fibrosis only	
20	N.C.	N.C.	Prol: harder	Exud: residual fibrosis only	
		Exud: slight clearing	Exud: clearing	Prol: harder	
				Exud: residual fibrosis only	

N.C. = No Change.
Exud. = Exudative lesion.
Prol. = Proliferative lesion.
Cav. = Cavity.

The fate of pulmonary
... Of the

N.C. = No Change.
Exud. = Exudative lesion.
Prol. = Proliferative lesion.
Cav. = Cavity.

The fate of pulmonary cavities during the treatment of these patients was variable. Of the 25 cavities initially visible, 8 were closed or lost to view, an additional 8 decreased in size and the remaining 9 were unchanged or larger. The changes noted by roentgenography were chiefly in the nature of resolution of the exudative components or hardening of the proliferative components. The extent, some organization or hardening of the proliferative components. The effect upon cavities, as has been said, was variable.

TOXICITY

A single case of severe exfoliative dermatitis due to streptomycin will be described below in some detail. With that exception and excluding, for the moment, reference to vestibular disturbance, no important toxic reactions were discovered in this series. Nausea and vomiting occurred early in the course of treatment in 2 patients, in one with sufficient severity to require a temporary reduction of the daily dosage from 1.8 to 1.2 g. In the first two weeks of treatment, 5 patients developed skin eruptions, chiefly maculo-papular, which disappeared in twenty-four to seventy-two hours with or without benadryl. An eosinophilia amounting to from 5 to 17 per cent was found periodically in 15 patients. In no case did a febrile reaction seem to be due to the drug. At intervals throughout therapy, albumin and casts were found in urine specimens from 8 and 10 patients, respectively, but in no instance was there sufficient renal damage to affect the urea clearance or the urea nitrogen concentration of blood serum.

All 20 patients developed some degree of vestibular nerve involvement. This appeared early in the fourth week of treatment and manifested itself by sensations of lightheadedness and vertigo which were often very marked. Caloric tests

revealed complete loss of rotary or lateral nystagmus following the instillation of ice water into the auditory canal in 15 patients (75 per cent). There has been no recovery of vestibular function, as judged by this objective test, either during the remainder of therapy or during the follow-up period of four months. The younger patients were able to compensate quite adequately for this loss, whereas the 2 patients who were more than 40 years of age were entirely unable to do so and are still as dizzy as they were at any time during treatment. Three patients complained somewhat of tinnitus at various times. No deafness was encountered although audiometric readings indicated mild and temporary interference with the function of the cochlear nerve in 2 instances. Our 21st patient, not included in tables 1 and 2 because his treatment had to be terminated on the thirty-second day, experienced some degree of deafness. His case is summarized because of the extremely severe toxic reaction which he suffered.

This patient's pulmonary tuberculosis, probably developed in March, 1946, was diagnosed on June 19, 1946, within a week before his entrance to our hospital. A left artificial pneumothorax was induced in July, and a left pneumonolysis was performed in August, 1946. Because the collapse was not made satisfactory by this procedure, the left pneumothorax was abandoned in September, 1946. Streptomycin therapy in a dosage of 1.8 g. a day was started on October 8, 1946, because of the exudative character of the pulmonary lesions and the failure to obtain satisfactory collapse.

The patient improved symptomatically within the first two weeks after starting drug therapy, with lessening of cough, improvement of appetite, and a weight gain of approximately 5 pounds in three weeks. His temperature fell to a range of 98° to 99°F. daily on the fourth day of drug therapy, a slight erythematous macular rash appeared on the anterior portion of his chest, neck and face. Benadryl, 150 mg. a day, was administered beginning on the second day of the rash, but, in spite of this, it became more extensive; his temperature mounted steadily from 100° on the day of the appearance of the rash to 104°F. three days later. Streptomycin was discontinued on the thirty-second day, three days after the rash appeared.

The patient appeared very ill, and six days after the rash appeared he was so deaf that he was only able to hear very loud sounds. The originally diffuse, erythematous rash, with small macular lesions on the face and anterior trunk, became progressively more wide-spread, red and swollen, until the entire skin surface was involved. He was given daily infusions of dextrose and saline solutions and benadryl was continued. By the fourteenth day of the dermatitis, the patient's skin began to desquamate, at first on the face and neck, and then on the trunk and limbs. The process of desquamation was nearly complete three weeks after the rash appeared, at which time the patient's temperature had fallen from an average of 103° to the vicinity of 99°F., and he was clinically much improved.

Complete renal and hematological studies did not reveal any considerable abnormalities during this reaction. There was a trace of albumin in the urine on one occasion but both blood urea nitrogen and nonprotein nitrogen concentrations were repeatedly normal. The percentage of eosinophils did not exceed 6. There was a leucocytosis of as high as 28,700 between the eighteenth and thirtieth day of the reaction. The erythrocyte sedimentation rate varied from 17 to 34 mm. per hour.

The patient did not regain grossly normal hearing until a month after the beginning of the rash. His skin regained normal appearance approximately a month and a half following the onset of the rash. It took months, however, for his toe and finger nails and hair, all of which had dropped off, to grow back.

The patient continued to run a fever of 100°F. or more following the disappearance of the rash. Increased cough and X-ray examinations indicated a spread of his pulmonary disease, chiefly in the left lung. He received pneumoperitoneum and left phreniclasia approximately two months after the onset of the dermatitis, but the pulmonary disease has progressed and is accompanied by a steady loss of weight and increased systemic symptoms. No attempt has been made to reinstate streptomycin therapy.

DISCUSSION

In evaluating the data on these patients one point stands out strikingly: In spite of the fact that 19 of the 20 patients were definitely progressing unfavorably prior to streptomycin treatment, as was demonstrated both by X-ray and by the appearance and symptoms of toxemia of the patients, not one showed an increase in his disease during the first three months of therapy and only 2 revealed a slight spread during its fourth month. Very definite symptomatic improvement occurred in 17 cases (85 per cent) and some degree of roentgenographic improvement in 16 cases (80 per cent). It would appear clear that the drug had inhibited, for the time being at least, the growth of bacilli in the body, for not only was the spread of the tuberculous process through the lungs retarded but some regression of the lesions occurred. Exudative processes responded better than productive ones. Strictly fibrotic and fibro-cavernous processes responded not at all.

Three relapses occurred during the 120-day follow-up period. The only severe one was in a large Italian-American (case 8), who had been extremely ill and failed rapidly prior to receiving streptomycin. He did exceptionally well while under treatment and his X-ray films showed considerable clearing of exudative disease. Three weeks after completing the 120-day course of streptomycin, the patient developed a cough which rapidly became severe and was productive of considerable mucopurulent sputum. He began to run a fever of 100°F. nightly, and later this became further elevated to from 101° to 102.6° F. He began to have small hemoptyses. An X-ray film of his chest revealed a soft pneumonic spread extending from the left hilar area in the lower lobe. There was a central area of rarefaction, indicative of tissue destruction (cavity formation). The patient was again given streptomycin in a dosage of 2.0 g. daily. At the end of two weeks he was not improved, either symptomatically or by roentgenogram, so the dosage was increased to 3.0 g. For a week he appeared slightly better on this regimen, but three weeks later neither radiological nor symptomatic improvement was apparent and the drug was discontinued. Sensitivity tests subsequently disclosed that his organisms were resistant to streptomycin at this time.

Two patients relapsed more than thirty days after the completion of therapy. One (case 10) has cleared on strict bed-rest alone; the other (case 3) had such a slight spread that a thoracoplasty on the original side has been done to obliterate the chief focus.

CONCLUSIONS

1. Streptomycin exerts an inhibiting effect upon *Mycobacterium tuberculosis* in man as evidenced by symptomatic relief, by cessation of spread of the disease process and, in some cases, by regression of the lesions on serial roentgenograms.
2. Exudative processes are more favorably affected than productive processes. Fibrotic and fibro-cavernous disease is not affected at all; a difference in response apparently due to the histopathological character of these latter processes, which cause a marked reduction in their blood supply and, hence, of the access of streptomycin to them.
3. In view of the loss of vestibular function which occurs in patients who receive streptomycin for long periods of time, it seems unwise to give the drug to patients with minimal disease.
4. Older patients do not compensate well for the loss of vestibular function and, as most of them have fibro-cavernous disease which does not, in any event, respond to the drug, very careful consideration should be given to each patient more than 40 years of age before prolonged streptomycin therapy is decided upon.
5. We do not feel that streptomycin is a cure for pulmonary tuberculosis nor do we believe it will supplant pneumothorax and certain other collapse measures in the majority of cases. It does appear to be of value in advanced disease, when the disease contains a large exudative component, either in helping to arrest the process or to clear up the exudative component so that a thoracoplasty may be carried out to close cavities which are unaffected by the drug.
6. It would appear that, since one of the chief dangers, if not the most dreaded danger, of pulmonary hemorrhage is the intrabronchial dissemination of viable tubercle bacilli through the lungs, streptomycin should be employed in severe pulmonary hemorrhage and the areas involved in the spread should be well saturated with it.
7. The drug, when given intramuscularly, is not free from toxic effects, such as nausea, vomiting, tinnitus, skin eruptions, agranulocytopenia (rare) and vestibular nerve involvement.

SUMMARY

Twenty patients with pulmonary tuberculosis, of whom 19 were showing progression of their disease with bed-rest or some form of collapse therapy, were treated for 120 days with streptomycin. Definite symptomatic improvement occurred in 17 (85 per cent) and some degree of roentgenographic improvement in 16 (80 per cent) patients. Some degree of vestibular dysfunction occurred in all 20 patients and, in 15, there resulted a complete loss of response to caloric stimulation which has not returned during the 120 days which have intervened since the conclusion of treatment. In the younger patients, however, this loss has been adequately compensated. One patient developed exfoliative dermatitis on his thirty-second day of treatment and the drug was discontinued. There have been 3 relapses during 120 days of observation. Only one of these has proved to be serious.

Streptomycin is not a cure but an adjunct to other treatment in carefully

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selected patients with pulmonary tuberculosis, particularly in those whose disease shows a predominantly exudative component.

SUMARIO

Tratamiento de la Tuberculosis Pulmonar con Estreptomina

Veinte tuberculosos pulmonares, 19 de los cuales revelaban agravación de su enfermedad con el reposo en cama o alguna forma de colapsoterapia, fueron tratados durante 120 días con estreptomina. En 17 (85 por ciento) hubo mejoría sintomática bien definida y en 16 (80 por ciento) alguna mejoría radiográfica. Em los 20 sobrevino alguna disfunción vestibular, y en 15 completa pérdida de la reacción al estímulo del calor que no ha retornado durante los 120 días transcurridos desde que terminó el tratamiento, aunque en los más jóvenes dicha pérdida está compensada adecuadamente. Un enfermo manifestó dermatitis exfoliativa al trigésimo-segundo día de tratamiento, suspendiéndose la medicación. Durante los 120 días de observación hubo 3 recidivas, pero sólo una resultó ser grave.

La estreptomina no es una cura sino un coadyuvante de otro tratamiento en enfermos cuidadosamente escogidos con tuberculosis pulmonar, y en particular en aquellos en que la enfermedad muestra predominio exudativo.

The authors wish to express their thanks to Dr. Meyer Gilbert and Dr. William L. Jenny for doing weekly calorie tests and audiograms on the patients, and to Dr. Stanton Hoechstetter for his interpretations of X-rays.

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STREPTOMYCIN THERAPY^{1,2}

With Special Reference to Pulmonary Tuberculosis

NICHOLAS D. D'ESOP³ AND JOHN E. STEINHAUS⁴

The Streptomycin Unit at Sunmount was inaugurated in the latter part of July 1946. At that time laboratory facilities for assaying streptomycin in blood, and for testing tubercle bacilli for streptomycin sensitivity were lacking at this Hospital; and we were fortunate to have these procedures done at the Research and Clinical Laboratory of Trudeau Sanatorium. In addition to the actual tests carried out in this laboratory the close association with its Director and his Associates afforded an excellent opportunity for the correlation of the laboratory and clinical data that were derived from the study.

MATERIAL

Twenty-six male patients with pulmonary tuberculosis were selected for therapy in part from Sunmount and in part from a large military hospital. There were, however, 8 patients in the latter group and one from Sunmount who had improved before streptomycin therapy was started. The 8 transferred patients were chosen for streptomycin therapy in May 1946, at which time it was thought unlikely that their pulmonary lesions would improve on further bed-rest and that they would, therefore, be suitable candidates for study. The fact that improvement had occurred by July 1946, when transfer was affected, illustrated the difficulty of selecting patients for streptomycin therapy. These 9 patients received streptomycin because therapy had been promised them and they were anxious to accept it. They will be considered briefly and separately in the evaluation of therapeutic results. There remain, then, 17 patients whose pulmonary lesions fulfilled the criteria set down in the protocol of this joint study.

The average age of the 17 patients was 28 years. Three were Negroes. Eleven patients were classified as far advanced and the remainder were moderately advanced. Eight of the 17 patients had shown progression of disease before streptomycin therapy, and 9 patients had lesions which were potentially unstable and which had not changed during a period of at least two months prior to therapy. Fourteen of the 17 patients, having had either progressive or unstable lesions while being treated with bed-rest alone, could have been treated with definitive collapse procedures (pneumothorax or thoracoplasty) only at the risk of important complications. The remaining 3 patients were reasonably good candidates for either type of collapse therapy and thus streptomycin was administered to those in a studied attempt to avoid pneumothorax or thoracoplasty.

¹ From the Department of Medicine and Surgery, Veterans Administration Hospital, Sunmount, New York.

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³ Chief, Medical Service.

⁴ Captain, M.C., A.U.S.

NICHOLAS D. D'ESOPPO AND JOHN E. STEINHAUS

Three patients with renal tuberculosis were also treated with streptomycin. One patient had far advanced, bilateral, renal involvement and impaired renal function before therapy was started. Therapy was discontinued on the seventeenth day because of renal insufficiency. A second patient had asymptomatic bacilluria without demonstrable anatomical or functional abnormalities. The third patient had severe dysuria, an abnormal urine sediment and persistent bacilluria.

DOSAGE AND DURATION OF TREATMENT

Patients in this series received 1.8 g. of streptomycin intramuscularly daily in individual doses of 0.3 g. every four hours during a period of 120 days. Two patients, however, were treated uninterruptedly for approximately 200 days, and 6 patients received a second course of streptomycin of variable duration. Four of these patients were retreated because of relapses, and the other 2 were retreated in order to learn whether further improvement would occur. At the time of retreatment the sensitivity of the bacilli of all 6 was known.

STREPTOMYCIN BLOOD LEVELS

Blood streptomycin was assayed by the method of Stebbins and Robinson (1) using staphylococcus SM strain. Specimens were obtained one and four hours following a dose of 0.3 g. of streptomycin. The average one-hour level was 19.3 mcg. per cc. of serum, and 78 per cent of all assays fell between 14 and 21 mcg. per cc. The average four-hour level was 11.1 mcg. per cc. and 87 per cent of all assays were between 8 and 14 mcg. per cc. One patient, who was being treated for renal tuberculosis and who had a previous nephrectomy, tended to have blood levels consistently higher than the average.

TOXICITY

When the streptomycin study at Sunmount was begun it was thought that the effects of streptomycin upon the kidney and the cochlear division of the eighth nerve were the toxic manifestations that should concern us most. It was curious that vestibular disturbance was accepted as one of the necessary, but probably unimportant, side effects of streptomycin therapy. As the study progressed it became apparent that the contrary was true. Significant renal damage occurred in one patient treated for renal tuberculosis, and partial hearing loss was recorded in one patient who had been treated for 200 days. On the other hand, significant vestibular damage occurred in an appreciable number of patients. We concluded, therefore, that at this dosage this particular toxic manifestation was probably the most important of all, and was potentially serious.

Renal function: Renal function, as measured by the kidneys' ability to excrete nitrogen, showed no impairment during 120 days of streptomycin therapy except in the one patient mentioned below. The 28 patients who completed the 120-day course of streptomycin had an average blood nonprotein nitrogen of 30.2 mg.

per cent before treatment, while the average blood urea nitrogen at the end of the study was 12.2 mg. per cent. Similarly, average values for the urea clearance were 85 and 105 per cent of normal, respectively. Occasionally, individual patients had blood urea nitrogens or nonprotein nitrogens slightly above the upper limits of normal, and these were difficult to interpret. However, streptomycin therapy was not discontinued in these cases, and repetition of the tests always revealed normal values. The one instance of renal insufficiency will be described in detail.

The patient, aged 55, had advanced bilateral renal tuberculosis. The renal function tests before streptomycin treatment were as follows: blood nonprotein nitrogen, 37 mg. per cent; urea clearance 41 per cent of normal; and phenolsulphonthalein excretion 47 per cent. On the seventh day of streptomycin therapy the patient developed an extensive rash and vertigo. Streptomycin was continued to the eighth day when therapy was stopped because the rash became more extensive. Blood streptomycin at this time was 90 mcg. per cc. Therapy was resumed from the twelfth to the seventeenth day with 1.2 and 0.9 g. daily, and hourly streptomycin levels during this time suggested almost no excretion. On the seventeenth day the urea clearance was 10 per cent of normal, and the blood nonprotein nitrogen was 63 mg. per cent. Streptomycin was discontinued. Periodic renal function tests since then (approximately one year) have shown urea clearances below 15 per cent of normal and blood nonprotein nitrogen of 60 to 80 mg. per cent. Examinations of the urine sediment have revealed numerous white cells, no casts, and no red cells. Proteinuria was present before streptomycin therapy and has continued essentially unchanged. There are no symptoms of uremia. This is an instance, then, of a patient with poor renal function who suffered serious renal damage as a result of streptomycin administration of brief duration at moderate dosage. It is interesting that renal insufficiency does not seem to have been progressive thus far.

Proteinuria occurred in 21 of the 28 patients who completed the 120 days of therapy. During the study 1,207 urine specimens were examined and proteinuria was found in 9 per cent of these specimens. In almost every case, the amount of protein was recorded as a "trace."

Cylinduria occurred at some time during therapy in every patient; it occurred in 14 per cent of all specimens. Casts were rarely abundant and were usually recorded as one to two in several high-powered fields of a centrifuged specimen. The relationship between cylinduria and alkalization of the urine was not studied.

The occurrence of proteinuria and cylinduria and the one instance of severe renal damage in this study indicate that streptomycin at this dosage is a nephrotoxic drug. Whether delayed renal injury will become apparent as time goes on cannot be predicted now; but thus far renal function tests during a post-streptomycin observation period of four to seven months have revealed no abnormalities. Apparently, significant renal damage can occur with this dosage in patients who already have impaired function before streptomycin is administered. In such cases it is probably wise to give test doses followed by blood streptomycin assays before regular, continuous administration is begun.

Skin: A maculo-papular eruption was noted in 5 patients and an erythema

nodosum-like lesion was observed in one patient. These were seen during the first two weeks of drug therapy. Streptomycin was discontinued in one patient because the eruption was becoming more extensive, and an exfoliative dermatitis was anticipated. Two unsuccessful attempts to desensitize the patient were made, and finally, after an interval of sixty days, streptomycin at the regular dosage was administered uneventfully. The skin lesion quickly disappeared in 4 patients without interruption of therapy and streptomycin was discontinued in the 6th patient because the eruption accompanied a more serious toxemic manifestation, namely, renal insufficiency.

Blood: An eosinophilia of 5 to 9 per cent occurred in 37 per cent of the total of 390 blood smears examined during this study; and an eosinophilia of 10 to 14 per cent occurred in 7.2 per cent of all examinations. Rarely were higher values recorded. There was no correlation between the occurrence and height of the eosinophilia and other toxemic manifestations. Leucopenia and anemia were not observed.

Eighth nerve impairment: Hearing loss, as determined by weekly audiometer readings, occurred in only one patient. The loss was of moderate degree and chiefly involved the higher tone range. It is significant that this patient, having relapsed, received streptomycin for 200 days almost uninterruptedly. During a post-streptomycin observation period of four months this patient's audiometric tests have indicated slight improvement in hearing.

Vestibular function: Disturbance of vestibular function was experienced by 25 of the 29 patients treated. Its onset occurred during the first six weeks of therapy (average, thirty-fifth day) and was heralded in most by vertigo, which was occasionally accompanied by nausea and vomiting. Uncertainty in walking, especially in the dark, and blurring of vision during sudden movements of the head, attended the vertigo. In individual patients these symptoms and the visible disturbance in gait were present to a very variable degree. But there was a clear relationship between the intensity of the initial symptoms and the severity of the subsequent locomotor defects. As streptomycin was continued, vertigo diminished and in most patients eventually disappeared. In some, however, it could still be evoked by sudden changes in the position of the head. Staggering and blurring of vision also became less pronounced as therapy was continued, and there remained a residuum of these symptoms that again tended to diminish further during the first few months following the cessation of therapy. It is these residual disturbances that assume importance in assessing this par-ticular toxemic manifestation of streptomycin. Objective testing of vestibular function was done only at the end of therapy. At that time it was noted that patients who had had vestibular symptoms of any degree whatsoever showed no nystagmus when the ear was stimulated with ice-water.

It is impossible to know whether the partial recovery of these vestibular disturbances was due to true restoration of damaged structures, or to the automatic training of compensatory mechanisms. The fact that improvement occurred rather rapidly in some patients as soon as more walking exercise was allowed would suggest the latter alternative.

It is difficult to estimate the importance of these residual vestibular disturbances, because opinion will vary as to what constitutes a significant loss. All will agree that a patient will have been seriously handicapped if he cannot walk without staggering, or if quick movements of his head while crossing a busy street result in blurring of vision. Lesser degrees of damage may allow necessary acts of this sort, but may still interfere with a patient's preferred occupation and ambitions. One patient in this group, for example, was a structural steel worker, and granting that his pulmonary lesion would allow his return to that occupation, it would undoubtedly be inadvisable, even though six months after the end of therapy vestibular loss can barely be detected in his behavior as a semi-ambulant patient. There is a component of this vestibular damage, however, that may have extremely serious consequences, namely, the blurring of vision that occurs during quick movements of the head. There are at least 6 patients who still experience this disturbance seven months following the end of streptomycin therapy. This disturbance occurred in 8 additional patients during therapy and completely disappeared even though therapy was continued. While it is impossible to know now whether these symptoms will be permanent, there is some likelihood that they will be. It is unnecessary to dwell upon the seriously disabling potentialities of this residuum.

Admitting that the evaluation of vestibular damage under conditions of sanatorium life is arbitrary, it may nevertheless be instructive to record such damage in the 29 patients who received streptomycin. We consider the disturbance in gait and the eye symptoms mentioned above as the simplest and most obvious criteria of vestibular loss. Damage was thought to be "severe" if, after an average post-streptomycin period of four to seven months, the gait was grossly abnormal or if the eye symptoms mentioned above persisted. The criterion for "moderate" damage was a gait that was noticeably abnormal only upon close inspection, and especially if the patient was known to have received streptomycin. Patients with "slight" disturbance were those who could walk perfectly normally with open eyes, but who might show some abnormality blind-folded, or under other conditions where compensatory mechanisms could not function. Under certain conditions, of course, these patients who now show "slight" damage might be significantly handicapped. Using these arbitrary criteria, there were in this group 9 patients with serious damage, 8 with moderate damage, 8 with slight and 4 with none.

It is clear that streptomycin administered at the dosage used in this study injures the vestibular centres to a potentially important degree in an appreciable proportion of patients. Only further observation of these patients will teach us how serious this damage will be; how much improvement and compensation will occur; and to what extent apparently minor residual damage will interfere with individual patients' occupational and social preferences. The incidence and degree of vestibular loss appear to be such, however, that we believe streptomycin at this dose should be withheld from patients with favorable disease, and those whose disease may be controlled by conventional methods of therapy. One of the encouraging features of this toxemic manifestation is the fact that it

appears to be almost certainly a function of dosage, or, rather, blood streptomycin concentration. Preliminary study of a group of patients now being treated with 1.0 g. daily suggests that important vestibular loss may occur only infrequently. It remains to be seen, however, whether this smaller dosage is as therapeutically effective.

OBSERVATIONS ON DRUG-FASTNESS

It has been clearly demonstrated that tubercle bacilli recovered from patients being treated with streptomycin are often able to grow in much higher concentrations of streptomycin than are obtained in the circulating blood even when maximal dosages are administered. It is not known whether such resistance to streptomycin represents adaptation in the Lamerckian sense, or whether certain bacilli are naturally resistant to streptomycin and simply outgrow the suppressed sensitive ones. Nor is there any clue as to why in some patients resistant bacilli are found during the early weeks of streptomycin therapy, while in others, resistance may not occur until after several weeks, or finally, why the bacilli of a few patients always remain sensitive. Whatever the mechanism may be, the phenomenon of bacillary resistance to streptomycin assumes great importance because it is reasonable to suppose that when bacilli become resistant, streptomycin will be therapeutically ineffective. Yet, this assumption has not been unequivocally borne out by clinical experiments. The problem is made difficult by at least two considerations: the fact that the type of patients selected for study very probably influences therapeutic results and relapse rate irrespective of bacillary resistance; and second, the fact that the majority of treated patients show resistant bacilli, and at the end of four months of therapy, for example, the group of resistant patients outnumbers the group of sensitive patients, thus making the evaluation of results statistically difficult until data about a large number of treated patients have accumulated.

In this study sputum and gastric washings were concentrated and then cultured upon tubes of Steenken and Smith potato-egg-yolk media. A representative portion of this growth was then tested for streptomycin sensitivity by the method of Wolinsky and Steenken (2). It will be realized that this method of testing for sensitivity required, on the average, eight weeks in this study. There is the disadvantage that the method used does not indicate what proportion of the bacilli in the original culture was sensitive and resistant. For if the development of bacillary resistance has therapeutic significance, then this deficiency in the method of measuring sensitivity may explain the continued improvement of certain patients whose bacilli have developed *in vitro* resistance. That is to say, the proportion of bacilli that is resistant may be small, and the suppression of sensitive ones by streptomycin may be reflected in clinical improvement. Yet, the method of testing sensitivity will show *in vitro* resistance. That is to say, The incidence of the development of resistant bacilli is shown in table 1. It will be noted that the bacilli obtained from all patients were sensitive to 0.5 mcg. of streptomycin per cc. of medium before therapy was started; 15 mcg. per cc. were chosen arbitrarily by us as the critical concentration which divided

resistant and sensitive cultures. That is, cultures that required 15 or more meg. per cc. of medium to inhibit growth were considered resistant, a concentration that approximated the average blood level obtained in this series. After one month of therapy, 13 per cent of those patients who still had positive cultures had become resistant; and at the end of two months, 44.5 per cent of positive cultures were resistant; and at the end of three and four months, resistant cultures had increased to 53 and 61 per cent, respectively. It is apparent, therefore, that the percentage of resistant cultures increased progressively as streptomycin

TABLE 1
Sensitivity to streptomycin of tubercle bacilli isolated from patients under treatment with 1.8 g. of streptomycin per day for four months

MICROGRAMS OF STREPTOMYCIN PER CC. OF MEDIUM NECESSARY TO INHIBIT GROWTH	BEFORE TREATMENT			AFTER 1 MONTH OF TREATMENT			AFTER 2 MONTHS OF TREATMENT			AFTER 3 MONTHS OF TREATMENT			AFTER 4 MONTHS OF TREATMENT		
	Number	Per cent of pos. cult.	Per cent of orig. 25	Number	Per cent of pos. cult.	Per cent of orig. 25	Number	Per cent of pos. cult.	Per cent of orig. 25	Number	Per cent of pos. cult.	Per cent of orig. 25	Number	Per cent of pos. cult.	Per cent of orig. 25
0.5 or less.....	25	100	100	16	69.5		7	39		4	23.5		3	17	
0.6 to 1.0.....	0			3	13		1	5.5		2	12		3	17	
2.0 to 5.0.....	0			1	4		2	11		0	0		1	6	
10.0 to 31.2.....	0			1	4		15	5.5		0	0		0	0	
60.0 to 125.....	0			0	0		3	17		2	12		2	11	
250 to 1,000.....	0			0	0		0	0		0	0		0	0	
Over 1,000.....	0			2	9	8	4	22	16	7	41	28	9	50	36
Total 1.0 or less....	25	100	100	19	83		8	44.5		6	35		6	33	
Total 5.0 or less....	25	100	100	20	87	80	10	55	40	8	47	32	7	39	28
Total 15 or more....	0	0	0	3	13	12	8	44.5	32	9	53	36	11	61	44
Total.....	25			23		18			17			18			

Presented by William Steenken, Jr. at the Third Streptomycin Conference of the Veterans Administration at St. Louis, May 1, 2 and 3, 1947.

therapy was continued. It will be noticed, in addition, that the rate of the development of resistance was greatest during the second month. If further study confirms the suggestion that the second month is indeed the critical period, and if clinical experiments reveal that the development of resistant bacilli is a disadvantage, then it is likely that six weeks may be chosen as the optimum period of therapy for the average patient. This will especially be true for those patients for whom streptomycin is being used as an adjunct to definitive collapse procedures.

From this small series we gained the impression that bacillary resistance to streptomycin was therapeutically significant, and might explain the symptomatic and roentgenological decline that some patients experienced in the later months

of treatment. It is realized that the results obtained in a small group of cases might be unusual, or might be influenced by the types of patients selected for treatment. For, if bacterial resistance has therapeutic significance, then it is reasonable to assume that, when a particular series includes a majority of patients with frankly progressive tuberculosis, poor results and relapses will occur when the bacilli of such patients become resistant. When, on the contrary, the bacilli in relatively stable patients, develop resistance, no untoward events may be expected; for the patients having profited temporarily by the suppressive effect of streptomycin, will again tend toward stability. We believe that these factors cannot be disregarded in the evaluation of the significance of resistance.

In this study the therapeutic significance of bacillary resistance was suggested, first of all, by the clinical behavior of certain patients. When the bacilli of these patients became resistant there was noted an increase in sputum amount, weight loss and fever. Constitutional and local symptoms tended to recur. There was, moreover, an excellent temporal relationship between this clinical decline and *in vitro* resistance. However, *in vitro* resistance was not always accompanied by these unfavorable events. Thus, bacilli of 11 of the 17 patients reported became resistant. Five of the 11 patients with resistant bacilli had an exacerbation of symptoms when resistance developed. It is probably significant that these 5 patients had had progressive pulmonary tuberculosis before streptomycin therapy, while the 6 patients who did not show an unfavorable trend clinically had had relatively stable disease.

A second type of evidence was the fact that *in vitro* resistance appeared to be reflected in the bacillary content of the sputum in some cases. Patients whose bacilli remained sensitive might have cavitation visible on X-ray films but sputum concentrates might be consistently negative. This was not observed in patients whose bacilli had become resistant. There was the additional observation that there was no instance of a patient in whom resistant bacilli developed, and who then went on to acquire persistently negative sputa as therapy was continued. That is to say, once bacilli became resistant, the sputum remained positive.

Röntgenological observations afforded further evidence that *in vitro* resistance might be more than an unrelated laboratory phenomenon. There were 4 patients whose cavities became smaller and then enlarged as streptomycin therapy was continued. This sequence of events was not observed in any patient whose bacilli remained sensitive. Again, there was a good correlation between the time the cavity enlarged and the time that *in vitro* resistance developed. In the second series of patients now being treated this observation has been amply confirmed, and we have come to look upon this change in cavity size as evidence, suggestive at least, of resistant organisms.

Thus far it has been suggested that *in vitro* bacillary resistance may be reflected in changes in symptomatology, in the bacillary content of the sputum and in the behavior of certain cavities. Yet, it is undoubtedly true that, while these unfavorable changes might occur, the proof of the therapeutic importance of resistance will rest upon the ultimate fate of the patient. And possibly the most

convincing evidence in this respect will be the results of retreating patients, who have suffered relapses, with known resistant and sensitive bacilli.

Four patients in this series contributed data to this end. Two patients with resistant and 2 with sensitive bacilli were retreated because of relapses. The 2 former patients had had rapidly progressive pulmonary tuberculosis, and both had improved markedly. But both had become worse at about the time that *in vitro* resistance developed, and further progression of disease occurred after the first course of therapy was completed. Upon retreatment they failed to improve and the progression of disease was not interrupted. One died of a massive pulmonary hemorrhage, and the other is now in the preterminal stage. The 2 patients who had sensitive bacilli were also retreated because of relapses following the first course of therapy. In the first patient a large right lower lobe cavity had become appreciably smaller during the first streptomycin course. Approximately forty-five days following streptomycin the cavity returned to its former size and retreatment was begun. The cavity decreased in size rapidly and could finally be demonstrated only by appropriate X-ray technique. Shortly after the end of the second course of therapy the cavity again enlarged. At this writing the patient is being retreated for a second time and there has been no symptomatic or roentgenological improvement. Sensitivity tests reveal that his bacilli were resistant to streptomycin before the third course of therapy was started.⁵ The second patient with sensitive bacilli who was retreated had a small spread four months following the end of the first streptomycin course. Upon retreatment the new lesion resolved almost completely; but it was so small initially that possibly this patient does not add much to the data we seek.

There were 2 additional patients with resistant organisms who were retreated. Both had had unstable lesions before the first course of streptomycin and in both a moderate amount of predominantly productive disease had cleared with little effect upon cavitation. One patient was retreated simply to learn whether further improvement would occur. He experienced no further symptomatic benefit and one of several cavities became larger. The other patient had shown an enlargement of cavity following the end of the first streptomycin course and was retreated for this reason. During retreatment the cavity at first became smaller and then enlarged. But most important was the fact that a new cavity developed in the contralateral lung.

Retreatment, then, of 4 patients with known resistant bacilli yielded poor results. Lesions in 2 had been progressive and these continued to progress. The other 2 relatively stable patients failed to improve further, and, indeed, were somewhat worse off than before. Retreatment of the 2 patients with sensitive bacilli, on the other hand, suggested that streptomycin was again effective. The patient who is now receiving the third streptomycin course, at a time when resistance as developed, appears to be especially instructive.

Finally, the behavior of patients with resistant and sensitive bacilli during and following therapy should be mentioned. These data can hardly be analyzed

⁵ This patient subsequently had a spread of disease during the second month of retreatment.

toward any definite conclusion because the number of cases was small and because 11 of the 17 patients developed resistant bacilli while they remained sensitive in only 6 patients. During streptomycin therapy unfavorable events were noted in 5 patients with resistant bacilli. These consisted of simple enlargement of cavity in 4 and spread of disease in one. During therapy none of the 6 patients with sensitive bacilli experienced unfavorable trends. Following the end of the streptomycin course, 8 of the 11 patients with resistant bacilli showed roentgenological evidence of relapse. These included enlargement of cavity in 3, enlargement of cavity plus spread of disease in 3, and reactivation of disease in 2, spread of disease was noted in one and reactivation of disease occurred in one. It is fairly clear that, during the administration of streptomycin, patients whose bacilli became resistant fared worse than those in whom they remained sensitive. In conclusion, we should like to suggest that there are probably two groups of patients who will furnish the most conclusive data concerning the significance of *in vitro* resistance. The first group includes those patients who had progressive pulmonary tuberculosis before therapy, and who, in addition, showed an unfavorable trend during therapy. If it is demonstrated that the majority of such patients developed resistant organisms then this will be strong evidence that *in vitro* resistance is a disadvantage. Improvement of pulmonary lesions during therapy is a much less reliable gauge, since some patients may do well in spite of drug resistance. The second group of patients are those who receive a second course of streptomycin because of relapses. Here again an unfavorable response to treatment in a majority of patients with resistant bacilli in contrast to a favorable trend in a majority of patients with sensitive bacilli will be significant.

THERAPEUTIC RESULTS

Clinical aspects: The symptomatic improvement that follows streptomycin therapy has been commented upon by all investigators and needs only brief confirmation here. Most patients in this study experienced decided symptomatic benefit within the first three weeks of therapy. Decrease in sputum amount occurred in most, appetite improved; most patients noted an increase in general strength and sense of well-being. Subjective improvement was undoubtedly influenced by the fact that patients were receiving a new and much publicized type of treatment. But the reduction in sputum amount and the decline in fever, which almost always accompanied symptomatic improvement, suggested that psychogenic factors were relatively insignificant. Two points relative to symptomatic changes during streptomycin therapy warrant emphasis. In the first place, it was observed that some patients experienced early symptomatic benefit wholly out of proportion to the meager retrogressive changes seen on serial X-rays films. One might have had the impression from observing such patients at the bed-side that vast improvement in the pulmonary lesions had occurred. Often this was not so. In general, this discrepancy was noted in patients whose principal lesion was cavitation. The early symptomatic improvement, we believe, indicates that streptomycin has

therapeutic potentialities, but has no direct bearing upon the ultimate fate of the patient being treated. This aspect of therapy, therefore, should be minimized. The second point we wish to make is the fact that the development of *in vitro* bacillary resistance was occasionally accompanied by a return of symptoms, an increase in sputum amount and weight loss. Indeed, as was mentioned before, this observation is suggestive evidence that the *in vitro* sensitivity test is not a laboratory artefact but has therapeutic significance. It is obvious, of course, that such correlation between the reversal of symptomatic improvement and the development of resistant bacilli, would be noticed only in these patients who had had symptoms initially. If our further experience finally convinces us that the continuation of therapy of patients with resistant bacilli is profitless, then it will be advantageous to be able to recognize resistance when the event occurs, rather than to wait until the laboratory is ready to demonstrate it.

Roentgenological aspects: While the prompt, and often startling, symptomatic improvement that follows streptomycin therapy suggests that streptomycin has therapeutic possibilities, it is nevertheless true that X-ray changes are a much more accurate gauge of its ultimate usefulness in the treatment of pulmonary tuberculosis. Though a patient, for example, may have become entirely asymptomatic and gained weight after two months of therapy, the X-ray may reveal that the pulmonary cavity, toward which treatment was directed, is still patent and merely reduced in size. When this occurs (as it frequently does) comparatively little has been accomplished, and the patient presents the same problem in therapy as before. But granting that X-ray study is the best single guide to changes occurring in the pulmonary lesions, it still has important subjective limitations. We have, nevertheless, selected certain elements of the total pulmonary disease as interpreted from the X-ray film and have attempted to assess the efficacy of streptomycin by the changes that were noted in these artificially isolated lesions. Thus, 6 of the 17 patients had lesions which were interpreted roentgenologically as being predominantly exudative (irrespective of a cavitary component). In all of these the trend of the disease had been progressive before streptomycin therapy was started. Resolution occurred to a greater or lesser degree in all 6. The rate and degree of clearing did not differ from that occasionally observed in certain patients who respond promptly to bed-rest treatment alone. These results then, were impressive because the lesions had been progressive before streptomycin therapy was begun. In several instances, cavities in the midst of such exudative disease, were merely reduced in size. The effect of streptomycin upon progressive exudative tuberculosis, in this small series was decidedly encouraging; especially since this type of disease is only poorly controlled by our present, conventional methods of therapy. And it would, therefore, appear that in this category at least streptomycin might be a useful acquisition to our therapeutic armamentarium.

There were 8 patients whose lesions were considered predominantly proliferative, though an exudative element was present in most. These lesions were potentially unstable and had shown no tendency to retrogress during a previous observation period of two to three months. In 6 of the 8 patients moderate to

excellent clearing of disease occurred during streptomycin therapy, and in the other 2 no appreciable changes were noted. As could be anticipated, the progressive clearing of the X-ray shadows was less marked than in predominantly exudative disease. The important consideration, we believe, is the fact that such predominantly productive, unstable lesions are frequently an obstacle to contralateral thoracoplasty, and it is encouraging that such lesions seem to be favorably affected by streptomycin.

Fourteen of the 17 patients had single or multiple cavities, which were larger than 2 cm. in diameter. X-ray films of 11 of the 14 patients revealed a reduction in size of cavities during the first two months of streptomycin therapy, but in only one instance did unequivocal cavity closure occur. Cavities less than 2 cm. in diameter could hardly be studied because planography was not available. Many such small cavities were suspected and the majority were "lost to view." But it was concluded that the interpretation of such shadows was untrustworthy and misleading. In 4 cases cavities decreased in size during the first one to three months of treatment and, then, enlarged even though therapy was continued. It is significant that all 4 patients developed resistant bacilli, and that these changes in cavity were not observed in patients whose bacilli remained sensitive. The behavior of cavitory disease was admittedly discouraging, but probably not surprising in view of the mechanical factors associated with most cavities.

Bacteriological aspects: All 17 patients were positive on smear before streptomycin therapy was started. At the end of treatment 13 patients had remained positive on smear, while 4 were positive on culture only. After an average follow-up period of seven months there remain 12 who are still positive on smear, 3 who are positive on culture only and 2 have negative cultures. It is probably true that these results are related to the fact that the prevalence of cavitory disease in the series was high, and that cavity closure occurred infrequently.

Evaluation of therapeutic results: There were 6 patients whose principal lesions before streptomycin treatment was begun were such that eventual thoracoplasty was the preferred conventional type of therapy, but who had contralateral unstable or progressive disease. After four months of streptomycin therapy these contralateral lesions had improved to the extent that roentgenologically, at least, thoracoplasty seemed feasible in 5. *In vitro* resistance had occurred in 4 of the 5. Thoracoplasty, however, was postponed because the post-streptomycin trend of the lesions was to be studied. During this observation period 3 patients had extension of disease. Two had resistant and the third had sensitive bacilli. It is interesting that the development of drug resistance did not seem to be disadvantageous, from the point of view of adjunctive collapse therapy, in the 4 patients with resistant bacilli.

There were 2 patients whose principal lesions warranted thoracoplasty but cavity was present in the contralateral lung. Both developed resistant bacilli, their cavities enlarged during and following therapy and one died of a massive pulmonary hemorrhage. Because streptomycin only infrequently affects cavity closure, it would seem that patients who are thoracoplasty candidates because of a lesion in one lung, but who have contralateral cavitation, will not often be brought to thoracoplasty by streptomycin therapy alone.

Two patients had destructive unilateral lesions which had shown recent progression. Most thoracic surgeons believe that recent disease of this sort contraindicates thoracoplasty, and the various interim procedures sometimes used to stabilize such lesions are frequently attended by important complications. During streptomycin therapy progression of disease was halted in both cases, but one patient developed resistant bacilli and had a relapse during the fourth month of treatment and a further increase in disease directly after therapy. Here again, it seemed likely that thoracoplasty might safely have been done after two months of streptomycin—at a time when bacilli were still sensitive. In the second patient the bacilli remained sensitive, the cavity decreased in size and then became larger approximately forty-five days after the end of the streptomycin course.

There were 3 patients with unilateral cavitory disease that was stable enough to warrant collapse therapy before streptomycin was begun. In these, streptomycin was used with the express purpose of avoiding collapse procedures. In 2 of the 3 patients the bacilli became resistant, their cavities were reduced in size during streptomycin therapy and have continued to become smaller during a seven-month post-streptomycin observation period. It is not yet certain that collapse therapy has been avoided. The third patient had a large cavity which closed.

There were 3 patients with progressive exudative pulmonary tuberculosis with a relatively minor cavitory component. One patient (a diabetic) improved to a remarkable degree symptomatically and roentgenologically; lesions have stabilized, and there remains one small cavity, less than 2 cm. in diameter by planography, in each lung. The exudative lesion in the second patient resolved to a moderate degree but reactivation of disease occurred two months following the end of therapy. This patient has been lost from observation. The third patient had an acute pneumonic lesion which resolved progressively during the four months of therapy. Two weeks later, however, he suffered a relapse of disease and was retreated for an additional three months. But he had developed resistant organisms during the fourth month of therapy and retreatment was entirely without benefit. He is now preterminal.

One patient with a complete thoracoplasty had a 2 cm. cavity in the contralateral lung. This was only slightly reduced in size during four months of therapy.

The present status of the 17 patients with pulmonary tuberculosis who fulfilled, in general, the requirements of the protocol may now be briefly summarized. They were observed for four to seven months following the end of streptomycin therapy.

One patient died and one is preterminal.

Three patients are undergoing thoracoplasty. One of these had an ipsilateral spread of disease during the fourth month and directly following the end of therapy. This was controlled by phrenic paralysis and pneumoperitoneum.

Two patients are suitable candidates for thoracoplasty.

One patient appeared to be a suitable candidate for thoracoplasty at the end of therapy but suffered contralateral reactivation of disease two months later.

Three patients apparently require no further treatment other than bed-rest at this time. One closed a large cavity during therapy. The other 2 have apparently closed cavities during a post-streptomycin period of seven months; but one of these has had a slight reactivation of disease in the contralateral lung.

Three patients are receiving pneumoperitoneum.

One patient is being retreated with streptomycin for the second time. His bacilli have become resistant and thus far the patient is not responding favorably.

One patient whose bacilli became resistant and who was retreated is receiving pneumothorax in preparation for contralateral thoracoplasty.

One patient has been lost from observation.

The 9 patients who were treated with streptomycin in spite of the fact that they had improved before therapy will be commented upon briefly. The 9 cases included 4 patients with predominantly cavitory disease, 4 patients with predominantly productive disease and one patient with an exudative lesion. Seven were moderately advanced and 2 were far advanced. Sputum before therapy was positive on smear in 5 and positive on culture in 4. All 9 patients continued to improve during streptomycin therapy, and the cavities of 4 patients closed. At the end of 120 days, 7 had become negative on gastric and sputum cultures, while the remaining 2 had become negative on concentrated smear but positive on sputum culture. After an average follow-up period of four months there were no relapses. Since the majority of these patients became negative on culture, study of the sensitivity of bacilli was incomplete. But, at any rate, no patient in this group developed resistant organisms. The impression was gained that at least 5 of the 9 patients improved during treatment somewhat more than could have been anticipated from their previous course. But such results, though suggestive, were hardly contributory to our study.

RESULTS IN RENAL TUBERCULOSIS

Two patients with renal tuberculosis completed the 120 days of streptomycin therapy. One patient had severe dysuria before treatment and this was completely relieved after approximately sixty days of therapy. He has now been observed for seven months following the end of treatment and there has been no

recurrence of symptoms. The urine is essentially negative. Urine cultures were usually positive for tubercle bacilli throughout the course of streptomycin and have continued positive to date. Bacilli remained sensitive to streptomycin. The second patient was asymptomatic before therapy and was treated because of persistently positive urine cultures. This remained positive during and after therapy. Bacillary resistance to streptomycin developed.

COMMENT

Streptomycin in the dosage used in this study appeared to be a reasonably safe antibiotic. While the renal toxicity cannot be disregarded, it was felt that vestibular damage was undoubtedly the most important toxic manifestation and was such as to contraindicate streptomycin therapy in patients whose pulmonary lesions may be controlled by conventional methods of therapy. However, it is quite possible that lower dosages may reduce the incidence and severity of vestibular damage—dosages now being investigated.

The results of this small series indicated that predominantly exudative pulmonary tuberculosis, and to a lesser extent, productive tuberculosis, were favorably influenced by streptomycin therapy. It should be emphasized that it was not the rate or degree of resolution of such lesions that were impressive, but rather the fact that these lesions had shown no tendency to regress during a previous observation period of bed-rest alone. These results, then, were decidedly encouraging. The incidence of cavity closure in this series was disappointingly low. But it should be recalled that only cavities above 2 cm. in size were evaluated. Possibly smaller cavities do close.

The results suggested that streptomycin is probably not definitive therapy for pulmonary tuberculosis, except possibly in cases of progressive exudative disease without significant cavitation. Its principal deficiencies are the failure of cavity closure in many instances, and the fact that bacillary drug resistance develops in the majority of patients treated for long periods of time. Yet the impressive gains made by some patients especially during the first two months of therapy justify the hope that a place for streptomycin will be found in the treatment of pulmonary tuberculosis. There are patients who present problems in therapy that are now but poorly solved by conventional methods of treatment. There is, for example, the patient who has a predominantly exudative lesion that progresses in spite of bed-rest. For this type of disease streptomycin may prove to be helpful, at least temporarily, and collapse measures, if indicated, may possibly be done more safely. Another common problem in therapy is the patient whose principal lesion makes him a candidate for eventual thoracoplasty, but who has, in addition, an unstable or progressive lesion in the contralateral lung. Procedures now employed to stabilize such patients for thoracoplasty are, on the whole, unsatisfactory. Streptomycin may possibly be useful in such cases. Other rather well defined problems in therapy that require investigation might be mentioned. This approach to the study of the value of streptomycin in the treatment of pulmonary tuberculosis should be pursued.

It was noted that during the third and fourth months of streptomycin therapy

a few patients lost the symptomatic and roentgenological gains that had been made in the earlier months; and that, in addition, unfavorable trends were seen in a considerable proportion of patients following the cessation of therapy. The impression was gotten (retrospectively, to be sure) that there might be an optimum time during the course of therapy when the institution of collapse procedures might have preserved what improvement had occurred. The use of streptomycin as an adjunct to collapse therapy may be modified to an important degree if *in vitro* drug resistance proves to be therapeutically significant. For there might well be an optimum duration of therapy—a period long enough for the desired therapeutic results to occur, and short enough to minimize the opportunity for the development of drug-fastness. Data, therefore, which will elucidate the therapeutic significance of drug-fastness are probably the most pressing need at the present time.

SUMMARY

1. Twenty-six patients with pulmonary tuberculosis and 3 patients with renal tuberculosis were treated with 1.8 g. of streptomycin daily for a period of 120 days.

2. The most significant toxic manifestation was vestibular dysfunction. There was one case of induced renal insufficiency.

3. Exudative pulmonary lesions and, to a lesser extent, predominantly productive lesions responded favorably. Cavity closure was infrequently observed. Conversion of sputum was uncommon. One patient with renal tuberculosis experienced complete symptomatic relief.

4. *In vitro* bacillary resistance occurred in 61 per cent of patients at the end of four months of therapy. Retreatment of relapsed patients indicated that *in vitro* drug resistance might be therapeutically significant.

5. The infrequency of cavity closure suggested the use of streptomycin as an adjunct to collapse procedure.

SUMARIO

La Estreptomycinoterapia en Particular en la Tuberculosis Pulmonar

1. A 26 enfermos con tuberculosis pulmonar y a 3 enfermos con tuberculosis renal se les trató con 1.8 gm. diarios de estreptomicina durante un período de 120 días.

2. La más importante manifestación tóxica consistió en disfunción vestibular. Hubo además un caso de insuficiencia renal provocada.

3. Respondieron favorablemente al tratamiento las lesiones pulmonares exudativas y, en menor grado, las de predominio productivo. El cierre de las cavernas fué raro, y otro tanto sucedió con la conversión del esputo. Un tuberculoso renal experimentó completo alivio sintomático.

4. Resistencia bacilar a la droga *in vitro* se presentó en 61 por ciento de los enfermos a los cuatro meses de terapéutica. El tratamiento de nuevo de las recidivas indicó que dicha resistencia *in vitro* puede revestir importancia terapéutica.

5. La rara oclusión de las cavernas sugiere el empleo de la estreptomicina como coadyuvante de la colapsoterapia.

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EDITORIAL

Case-Finding

Modern case-finding is without doubt one of the chief factors in the battle against tuberculosis. It began with emphasis upon contact examinations and extended to mass or even total community case-finding techniques. Latterly the roentgen technique, particularly as exemplified by the miniature film, has for obvious reasons tended to crowd other methods, notably tuberculin, quite out of the picture.

Nevertheless there are enormous difficulties in the way of procuring periodic chest films for everybody. Expense is one thing; personnel is another. Coöperation on the part of the public, while less tangible, is not to be ignored. As an experiment, total community surveys have been made and are now being undertaken by the Tuberculosis Division of the United States Public Health Service. Meanwhile it would seem that other efforts, in an attempt to focus roentgen case-finding technique, should not be neglected.

Fortunately it has long been recognized that tuberculosis is distributed in more or less well-defined patterns. It is more prevalent among the underprivileged; therefore, in certain racial groups whose housing and nutrition are bad, as for example the Negroes, the Chinese and the Mexicans. Epidemiological and experimental observations indicate that race *per se* plays a rather important rôle in morbidity and mortality characteristics. That these differences are not chiefly determined by race, however, is suggested by numerous observations among which may be mentioned the fact that the Chinese of San Francisco have a death rate between three and four times that of the white population, while the Japanese of the same city, in the year before World War II, had a death rate less than that of the white population. As far as the white population is concerned, it is well known that the death rate increases in inverse ratio to economic status. Case-finding studies, therefore, yield rich returns when directed toward such groups.

Recently it has been recognized that there exist in this country concentrating mechanisms which are normally operative. As an example, the work of Hodges and others has brought general hospitals to the attention of tuberculosis workers.¹ As a result, we have recently witnessed a determined campaign to secure routine roentgen chest examinations of some sort for all general hospital admissions.

Less consideration has been given the offices of the general medical practitioners. A splendid pilot study by Dr. Albert C. Daniels, then a general practitioner in San Rafael, Marin County, California, has received less than the attention it deserved.² Begun in 1941 and continued until Doctor Daniels was commissioned in the Navy in 1942, it suggested that an alert general practitioner

¹ FRED JENNER HODGES: Fluorographic examination of the chest as a routine hospital procedure, *Radiology*, 1942, 38, 453.

² ALBERT C. DANIELS: Routine chest fluoroscopy in general practice, *Tuberculosis Supplement*, California & West. Med., 1942, 57, 44.

can contribute measurably to the solution of the tuberculosis problem in his community. While the Daniels figures are small they are nonetheless suggestive. Between October, 1941 and April, 1942, Doctor Daniels routinely fluoroscoped 250 patients which included all new patients who passed through his office during this period; 14"x17" films were taken of all patients who showed suspicious findings on fluoroscopy. Seven active cases of pulmonary tuberculosis were discovered in this group of 250 patients, a prevalence of 2.8 per cent. They varied in age from 18 to 57. None gave a history of close contact. Only one suspected that he might have tuberculosis; only one had physical signs suggestive of pulmonary disease.

In the seven previous years of general practice, Daniels had discovered only 5 active cases of pulmonary tuberculosis. Other physicians of the community, queried by Daniels, stated that they discovered one or two active cases of pulmonary tuberculosis a year. Nevertheless, in this community, statistics suggest that approximately 30 per cent of the general population consult some physician during the year for some complaint.

Daniels assumed at this time that the prevalence of clinically significant tuberculosis in the population at large in his community was 1 per cent. This would have meant that there were approximately 500 cases existing in the county. If the prevalence of 2.8 per cent of active cases in his practice were generally applicable to other doctors' offices, then in the 15,000 patients who consulted doctors there should have been about 400 cases of tuberculosis, or about four-fifths of the active disease in the community. At least in this area it is at once suggested that a modern case-finding program carried out by general practitioners by any recognized roentgen technique would go a long way toward the solution of the local tuberculosis problem.

Recognizing, then, that clinics, general hospitals and doctors' offices represent great natural sieves, constantly operative day in and day out, concentrating tuberculous individuals, there is present here an extremely economical method of attack as well as a peculiarly fitting device to bring the general physician and organized medicine into the tuberculosis picture.

It seems to the writer that the general practitioners' offices of this country are the great neglected field for case-finding and may prove to be one of the most economical and satisfactory places for further effort. The crux of the matter lies in establishing coöperation between Tuberculosis Associations, the Public Health Services and organized medicine. This may seem a difficult task, yet its full accomplishment would draw into active coöperation in the antituberculosis movement every general practitioner of medicine in the United States.

Pilot studies on scales larger than the Daniels survey are now underway. These are being undertaken with the aid of the United States Public Health Service and local health authorities in California and elsewhere on a private basis. These patients secure a miniature film the same way that they would normally secure a blood count or urinalysis. Organizing to begin the survey is the most difficult part of the problem. Perhaps the best way for Tuberculosis Associations to begin is to secure the coöperation of a local physician who agrees to have roent-

EDITORIAL

gen examinations of every patient for a given length of time, possibly three to six months, after which the local problem can be evaluated. The advisability of making available such examinations for this highly selected group can then be determined.

Admittedly a serious weakness in many case-finding techniques has been their inclusion of such a large part of the healthy segment of the population. Preliminary figures derived from 350,000 miniature films taken in California during the past year reveal a prevalence of only half of one per cent or about one-sixth of the Daniels figure. A further weakness is the periodicity of these techniques. Hospitals, clinics and physicians' offices furnish a constantly functioning service which we can ill afford to neglect.

SIDNEY J. SHIPMAN

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AMERICAN TRUDEAU SOCIETY

With profound sorrow the Council of the American Trudeau Society, Medical Section of the National Tuberculosis Association, has learned of the deaths of twenty-four members during the period June, 1946 to May, 1947. Among this group were several physicians who had played significant rôles in the development of the Society. All were valued members, and therefore, be it

RESOLVED: That as a tribute to those who are no longer with us, this expression of sorrow be published in the *AMERICAN REVIEW OF TUBERCULOSIS*, and that their names be recorded for the information of those not present at the meeting in San Francisco, June, 1947.

With deep regret, the Council announces the passing of the following members:

Edward R. Baldwin, M. D., New York
Alford L. Briskman, M. D., Kentucky
Harold W. Campbell, M. D., Pennsylvania
Leroy U. Gardner, M. D., New York
Fred H. Heise, M. D., New York
Harwood L. Hollis, M. D., New York
Samuel H. James, M. D., California
Drue King, M. D., Alabama
Linda Bartels Lange, M. D., Pennsylvania
George A. Lassman, M. D., New York
Yvon Laurier, M. D., Canada
Emanuel Libman, M. D., New York
Paul P. McCain, M. D., North Carolina
Torrence C. Moyer, M. D., Nebraska
Ira D. Nelson, M. D., New Mexico
C. A. O'Quinn, M. D., Florida
Siebert Proskauer, M. D., New Jersey
Michael Smith, M. D., Florida
H. I. Spector, M. D., Missouri
Arthur Bruce Steele, M. D., California
Frederick Douglass Stubbs, M. D., Pennsylvania
Lucius N. Todd, M. D., Georgia
James Guy Van Scoyoc, Sr., M. D., California
Daniel Yellin, M. D., California

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will be mailed with the January, 1948 issue of the REVIEW.